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Overdiagnosis associated with breast cancer screening: A simulation study to compare lead-time adjustment methods

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ABSTRACT

Objective: Estimating overdiagnosis associated with breast cancer screening may use annual incidence rates of cancer. We simulated populations invited to screening programmes to assess two lead-time adjustment methods.
Methods: Overdiagnosis estimates were computed using the compensatory drop method, which considered the decrease in incidence of cancers among older age groups no longer offered screening, and the method based on the decrease in incidence of late-stage cancers.
Results: The true value of overdiagnosis was 0% in all the data sets simulated. The compensatory drop method yielded an overdiagnosis estimate of −0.1% (95% credibility interval −0.5% to 0.5%) when participation rates among the population and risk of cancers were constant. However, if participation rates increased with calendar year as well as risk of cancer with birth cohorts, the overdiagnosis estimated was 11.0% (10.5–11.6%). Using the method based on the incidence of early- and late-stage cancers, overdiagnosis estimates were 8.9% (8.5–9.3%) and 17.6% (17.4–17.9%) when participation rates and risks of cancer were constant or increased with time, respectively.
Conclusion: Adjustment for lead time based on the compensatory drop method is accurate only when participation rates and risks of cancer remain constant, whereas the adjustment method based on the incidence of early- and late-stage cancers results in overestimating overdiagnosis regardless of stability of participation rates and breast cancer risk.

1. Introduction

From a public health perspective, the benefit of a breast cancer screening programme in terms of mortality reduction must outweigh its harms including overdiagnosis, i.e. the detection of cancers that would never have clinically surfaced in the absence of screening [1,2].

Besides differences in participant characteristics and screening programmes, methodological issues might explain the wide variations of overdiagnosis estimates published [3–6]. Basically, quantifying overdiagnosis is based on a comparison of incidence for screened and unscreened populations. An increase in the incidence of cancer following the implementation of a screening programme can be explained by three potential mechanisms [7]. First, sudden changes in the prevalence of risk factors may occur contemporaneously with the screening programme. Second, lead-time increases incidence rates due to the earlier date of diagnosis for screen-detected cancers. Third, incidence may be increased by overdiagnosis. Consequently, unbiased overdiagnosis estimates require adjustment for changes in the underlying incidence of cancer when a comparison of incidence before and after the implementation of screening is carried out, as well as adjustment for lead time.

The most reliable estimates of overdiagnosis come from randomized controlled trials comparing cumulative incidence of cancer between screened and unscreened groups. This estimate is correctly adjusted for lead time if the duration of the follow-up period after the end of screening is adequate and if no screening occurs after the end of the nominal invitation period. However, cross-sectional data from population-based cancer registries are widely used to compute annual incidence rates in

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populations offered screening. In this case, three approaches for adjusting for lead time coexist [8]. The first approach consists in postponing the diagnostic dates of screen-detected cancer for a period of time corresponding to the estimated lead time [9,10]. The second approach considers that the initial increase in breast cancer occurrence in a cohort of screened persons due to lead time would be fully compensated by a similar decrease in cancers among older age groups no longer offered screening, the so-called compensatory drop, if there is no overdiagnosis [11]. In the third approach, the increase in the incidence of early-stage cancers and the decrease in the incidence of late-stage cancers during the same period are used to account for the effect of lead time [12].

The accuracy of different lead-time adjustment methods using simulated data was studied by Duffy and Parmar [13]. They postulated populations with constant incidence and participation rates and observed that a long-term follow-up after the end of the invitation period was required to avoid residual lead-time effects using the compensatory drop approach. However, the accuracy of this approach remains unknown in the context of changes in underlying incidence and participation rates. Moreover, the accuracy of the adjustment for lead time using early- and late-stage cancers has not been assessed in the situation where the true rate of overdiagnosis is known, i.e. using simulated data.

Using a simulation-based study design, we aimed to assess the accuracy of the two lead-time adjustment methods that did not assume specific values for lead time, i.e. the compensatory drop method and the incidence of early- and late-stage cancers, to estimate overdiagnosis using annual incidence rates.

2. Methods

2.1. Model overview

We refined a previously developed microsimulation model designed to estimate overdiagnosis associated with mammography screening [14]. The occurrence of cancer and its diagnosis were simulated in birth cohorts comprising one million people. We specified a lifetime of 80 years for all individuals in order to prevent overdiagnosis resulting from competitive causes of death. For each birth cohort, the lifetime risk of cancer was specified. When a cancer occurred, the age at onset of the pre-clinical phase and its length (the sojourn time) were simulated. All simulated tumours were progressive, evolving towards the presence of clinical symptoms. Two types of pre-clinical phases of cancers were considered. First, the tumour remained in an early stage during the pre-clinical phase and clinical signs appeared during the early phase. Second, the tumour evolved to a late stage during the pre-clinical phase and clinical signs occurred at the late stage.

The screening programme targeted individuals aged 50–69 years who were offered screening every 2 years. We considered that cancers were screen-detected if they were in their pre-clinical phase at the time of the screening test, taking into account a 90% test sensitivity.

2.2. Model parameters

A total of seven different situations were simulated (Table 1). Three populations were used as references to compute cross sectional incidence rates for each calendar year without participation in screening when the lifetime risk of cancer was constant (situations 1 and 4) or increased with birth cohorts (situation 6). In base-case analysis, we simulated a constant 10% lifetime risk of cancer across consecutive birth cohorts and constant participation rates of 50% across the calendar year (situation 2). In sensitivity analysis, participation rates were 80% (situation 3), sojourn time values were 1.5 times higher (situation 5) and lifetime risk of cancer varied from 10% for the 1900 birth cohort to 20% for the 1950 birth cohort, whereas participation rates increased from 20% at year 0–80% at year 15 (situation 7). Two types of cancer were considered: some cancers remained in the early stage during the entire pre-clinical phase, whereas others evolved from early to late stage during the pre-clinical phase.

2.3. Computation of incidence rates

We computed cross sectional annual incidence rates of cancer in a population aged 50–69 and for 5-year age-specific incidence rates from 50–54 to 70–74 years during a period of 24 calendar years (from year −8 to year 15 inclusive, with year 0 corresponding to the start of the screening programme). We compared cross sectional incidence rates in populations invited to screening from year 0 with participation rates ranging from 20% to 80% and in a similar population not offered screening to highlight the effect of lead time on incidence rates.

2.4. Estimating overdiagnosis

The true value of overdiagnosis in the simulated population was 0% for participants because we excluded the two components of overdiagnosis, i.e. the competitive causes of death and the presence of non-progressive tumours, by simulating only progressive tumours in individuals dying at 80 years.

Estimates of overdiagnosis were based on a comparison of annual incidence rates in populations invited to screening with participation rates ranging from 20% to 80% and in a population not offered screening during the same period. As reported by others [11], the analysis was restricted to the year 4 to year 15 period to avoid the prevalent peak of incidence during the first years of screening.

Table 1
Characteristics of simulated populations.

Situation	Lifetime risk of breast cancer (%)	Sojourn time (years)		Participation rate in screening (%)
		For cancers with pre-clinical phase including only early stage	For cancers with pre-clinical phase including early and late stage	
1	10%	3 (early stage)	2 (early stage) / 2 (late stage)	0%
2	10%	3 (early stage)	2 (early stage) / 2 (late stage)	50%
3	10%	3 (early stage)	2 (early stage) / 2 (late stage)	80%
4	10%	4.5 (early stage)	3 (early stage) / 3 (late stage)	0%
5	10%	4.5 (early stage)	3 (early stage) / 3 (late stage)	50%
6	10–20%	3 (early stage)	2 (early stage) / 2 (late stage)	0%
7	10–20%	3 (early stage)	2 (early stage) / 2 (late stage)	20–80% (year 0 to year 15)