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Original article

Overdiagnosis and overtreatment associated with breast cancer mammography screening: A simulation study with calibration to population-based data

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ABSTRACT

Objectives: The magnitude of overdiagnosis of breast cancer associated with mammography screening remains controversial because of methodological issues. The objective of this study was to quantify overdiagnosis and overtreatment associated with a population-based screening programme, taking into account lead time and uncertainty concerning baseline incidence of breast cancers.

Material and methods: A simulation model was developed to replicate incidence and detection rates of breast cancer observed in the Isère Département, France. The parameters of the model were estimated using an approximate Bayesian computation method.

Results: For women aged 50–74 years during the 2007–2010 period, overdiagnosis of non-progressive breast cancers accounted for 17.0% (95% credibility interval (CI): 2.5%–35.5%) of all in situ cancers diagnosed, 5.5% (95% CI: 0.8%–9.8%) of all invasive cancers diagnosed, and 20.3% (95% CI: 3.0%–38.9%) of in situ and 13.0% (95% CI: 2.2%–23.3%) of invasive screen detected breast cancers. The estimates of overdiagnosis due to competitive causes of death were 1.0% (95% CI: 0.2%–%1.7) and 1.1% (95% CI: 0.6% –1.7%) for all in situ and invasive cancers diagnosed, respectively, and 1.3% (95% CI: 0.2%–2.0%) and 2.6% (95% CI: 1.4%–4.0%) of all in situ and invasive screen detected breast cancers, respectively.

Among 1000 screen-detected cancers in 2010, 155 (95% CI: 27–284), 134 (95% CI: 10–242) and 140 (95% CI: 25–254) women underwent breast conserving surgery, lymph node dissection and radiation therapy for overdiagnosed cancers, respectively.

Conclusion: Our estimates of overdiagnosis should be balanced against the reduction of breast cancer mortality to assess the value of breast cancer screening programme.

Introduction

The benefits of mammography-based breast cancer screening programmes are well established by meta-analyses of randomised trials which have demonstrated a reduction of breast cancer mortality [1,2]. However, such programmes are also associated with side effects including overdiagnosis, i.e. the detection of cancer that would never have been clinically apparent in the woman's lifetime without screening, and overtreatment, i.e. treatments carried out for overdiagnosed cancers [3].

Two mechanisms can explain overdiagnosis [3]. First, some cancers may never progress to become clinically detectable and consequently remain in a pre-clinical phase. Second, women may die from another cause of death than breast cancer during the pre-clinical phase, before the cancer becomes clinically detectable.

The published estimates of overdiagnosis associated with population-based screening programmes, expressed as the percentage of the expected incidence in the absence of screening, varied from

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less than 5% to more than 50% [4]. The estimates of overtreatment are also controversial, with conflicting results on the variation of the number of mastectomies performed in a population invited to screening [1,5,6] and the difficulty disentangling the consequences of overdiagnosis and lead time on the types of treatments provided.

Adjustment for lead time, i.e. the period between the point in time when early diagnosis with screening is made and the point in time when the diagnosis based on symptoms would have been made, and estimation of the baseline incidence that would have been observed without screening are the two main methodological issues when estimating overdiagnosis [4]. An unbiased method would be based on data from randomised controlled trials comparing the cumulative incidence of cancers between two groups of women, a group of women invited to screening and a control group, with a follow-up period after the last invitation long enough to adequately adjust for lead time. However, persisting participation in mammography screening after the end of invitation to the screening group as well as end-of-trial participation in the control group can bias the adjustment for lead time. Moreover, most trials were conducted several decades ago when the effectiveness of treatments and the mammography technology were different.

Using data from population-based programmes presents the advantage of estimating overdiagnosis in current screening programme settings. However, the lack of data from a control group implies methodological issues including adjustment for lead time and estimating the baseline incidence. One solution comes from simulation models calibrated to observational data which allow adjustment for lead time by modelling the duration of the pre-clinical phases of cancer and take into account the uncertainty concerning the natural history of the disease as well as participation rates in individual screening [7]. We previously reported a simulation model designed to estimate overdiagnosis only due to non-progressive cancers in the Isère Département, France, during the 1991–2006 period [8]. However, the mammography technology has improved since 1991 and our previous estimates of overdiagnosis may not apply to the current settings of the screening programme.

The primary objective of this study was to estimate overdiagnosis associated with mammography screening in a recent period, distinguishing overdiagnosis due to non-progressive cancers and overdiagnosis due to other causes of death than breast cancer. The secondary objective was to estimate overtreatment for early-stage cancers.

Methods

Study design and settings

We developed a simulation model designed to replicate incidence and detection rates of breast cancer in the Isère Département, a French administrative entity with nearly 1.2 million inhabitants. In this Département, a breast cancer screening programme started in 1991 and women aged 50–74 have been invited biennially since 2002.

Data collection

Data concerning breast cancers diagnosed in Isère and participation rates in organised breast cancer screening were obtained from the population-based cancer registry covering the Isère Département and from the Office De Lutte contre le Cancer (ODLC), which coordinates cancer screening in Isère. A supplementary collection of data in medical files from hospitals and physicians was carried out when information was missing.

The stage was classified according to the TNM classification [9] distinguishing carcinoma in situ, early-stage invasive cancers defined as tumours located in the breast (T1N0M0, T2N0M0 and T3N0M0) and late-stage cancers including tumours with involvement of the chest wall or the skin (T4), the lymph nodes (N1 to N3) and distant metastasis (M1). Due to feasibility issues associated with the collection of data in medical files, we only studied the treatments provided for cancers diagnosed in 2010.

Model

- Overview

We simulated all-cause mortality, the occurrence of breast cancer and its natural history, as well as participation in screening in a population born between 1933 and 1960 to obtain all events related to screening participation, cancer detection and deaths among women aged 50–74 during the 2007–2010 period. The simulation model involved 13 parameters (Supplementary Table 1) determining the risk of breast cancer for a given birth cohort (four parameters), the age at onset of cancer (two parameters) and its natural history (five parameters) including the presence of non-progressive cancers, as well as participation rates in screening (two parameters). Model assumptions are summarized in Supplementary Table 1. Basically, for each woman the simulation started by determining the date of death, then the presence of a breast cancer during her lifetime, as well as breast cancer type and its natural history with the length of pre-clinical phases. Finally, participation in biennial organized and individual mammography screening was determined. Appendix 1 reports details of the events simulated for each women.

- All-cause mortality

Survival times were generated for all individuals using a simulation model calibrated to mortality rates observed in women who lived in Isère in 2010 [10].

- Natural history

Five different types of pre-clinical phases were assumed (Fig. 1). We hypothesised that late-stage invasive (T4, N1 to N3 or M1) would always evolve to a clinical phase. Consequently, we considered that non-progressive cancers, i.e. cancers that remain in a pre-clinical phase, could only be classified as T1N0M0, T2N0M0 and T3N0M0.

- Diagnosis

Breast cancers might be detected either clinically or by screening mammography depending on their natural history, participation in screening and mammography sensitivity.

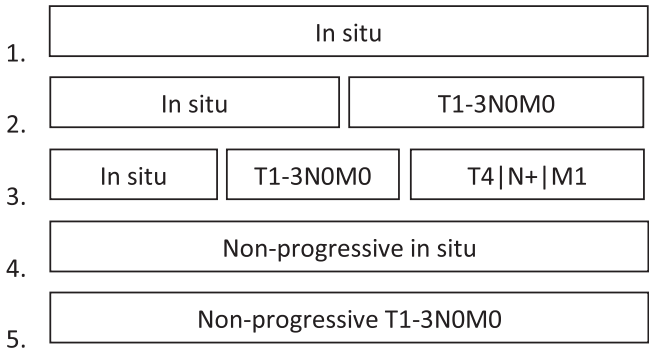

Fig. 1. Types of pre-clinical phases of breast cancer included in the simulation model.