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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.

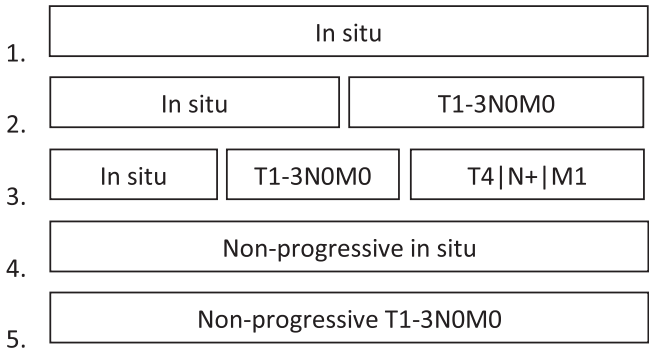

Fig. 1. Types of pre-clinical phases of breast cancer included in the simulation model.

Statistical methods

- Incidence and detection rates in Isère

We computed incidence and detection rates for in situ, early-stage and late-stage breast cancer. Incidence rates were computed as the number of cancers diagnosed per 100,000 women aged 50–74 years during the 2007–2010 period. Detection rates were defined as the number of screen-detected cancers among participants in the first round of screening (prevalent screen) and among participants in the second round of screening (incident screen) for 10,000 women during the 2007–2010 period. We restricted the computation of detection rates among women aged 50–54 to exclude women who participated in other organized screening programmes before a move in Isère.

- Estimate of overdiagnosis

The 13 parameters in the model were estimated using an approximate Bayesian computation (ABC) method. For complex problems with computationally intractable likelihoods, ABC approaches bypass exact likelihood calculations by using simulations and rejection sampling based on summary statistics [11]. Summary statistics were computed as annual incidence rates representing the only information available in the study.

In practice, the proportion of overdiagnosis due to non-progressive cancer and competitive causes of death was determined by calibrating the model to the incidence rates of carcinoma in situ, early-stage invasive cancers and late-stage invasive cancers, observed during the 2007–2010 period in Isère. We first simulated 100,000 data sets each comprising 245,000 women, with model parameters drawn from prior distributions (Supplementary Table 2). For each simulated data set, we computed a set of summary statistics, including incidence rates for carcinoma in situ, early-stage invasive cancers and late-stage cancers. Then we retained 100 (0.1%) data sets with the smallest Euclidean distance between the simulated and observed values of incidence rates. The values of the parameters were then corrected to form an approximate sample from the posterior distribution [12]. The posterior predictive distributions of overdiagnosis were calculated among all cases of breast cancers diagnosed and among all breast cancers detected by screening mammography. The methodology was similar to the ABC approach used in a previous paper [8].

Overdiagnosis due to non-progressive cancers and competing mortality was estimated over the full age span 50–74 even if all women were not followed-up from 50 to 74, since we included in the analysis all women aged 50–74 during the 2007–2010 period.

Our estimates were adjusted for lead time by attributing a lead time to screen-detected progressive cancers only.

- Estimate of overtreatment

Estimates of overtreatment were obtained by applying the proportion of the different types of treatments provided in 2010 for in situ and early-stage invasive cancers to the estimates of overdiagnosis among screen detected cancers obtained previously.

All data sets were generated with a computer programme developed specifically for our application and approximate Bayesian inference was performed with the ABC package [13] in the R statistical software, version 2.12 (R foundation for statistical computing, Vienna, Austria).

Results

Participants in organized screening

During the 2007–2010 period, age-specific participation rates were 47.9%, 52.4%, 52.0%, 52.0% and 43.9% for women aged 50–54, 55–59, 60–64, 65–69, 70–74, respectively. Among participants in screening, 30.9% of women underwent prevalent screens during this period. Digital mammography was authorised in 2008 in the breast cancer screening programme and represented 0.0%, 14.6%, 42.0% and 53.2% of the total of organized screening mammograms in 2007, 2008, 2009 and 2010, respectively. Seventy two percent of participants were aged 50–64.

Incidence and detection rates in Isère

A total of 387 carcinomas in situ and 2010 invasive cancers were diagnosed during the 2007–2010 period among women aged 50–74 years, corresponding to incidence rates of 61.1 per 100,000 for carcinomas in situ, 316.9 per 100,000 for invasive cancers, including 204.6 per 100,000 for early-stage invasive cancers and 112.3 per 100,000 for late-stage invasive cancers.

At prevalent screen, detection rates were 19.0 and 68.3 per 10,000 women screened for in situ and invasive cancers, respectively, whereas at incident screen, detection rates were 17.5 and 34.9 per 10,000 women screened for in situ and invasive cancers, respectively.

Prior and posterior distributions of model parameters

Prior and posterior distributions of the 13 parameters are shown in Supplementary Fig. 1 and Supplementary Table 2. Several posterior estimates were correlated. The lifetime risk of cancer for women born in 1900 was negatively correlated with the increase of the lifetime risk for women born in 1900 and 1950. The lifetime risk of non-progressive in situ cancers was negatively correlated with the length of preclinical phase of in situ progressive cancers, and positively correlated with the proportion of in situ cancers that evolved to invasive cancers during the preclinical phase. No obvious correlations were observed for the lifetime risk of invasive progressive cancers and other parameters.

Predicted incidence and detection rates

All incidence rates observed in Isère were included in the interquartile range of predicted incidence rates (Fig. 2). Although the model was not calibrated on detection rates, observed detection rates were also included in the interquartile range of predicted detection rates except for invasive cancers at prevalent screens (Fig. 3). Indeed, the observed detection rate of invasive cancers at prevalent screens (68.0 per 10,000) was higher than the median value (53.2 per 10,000) and the 75th percentile (60.7 per 10,000) of predicted detection rates.

Overdiagnosis estimates

All overdiagnosis estimates are reported in Table 1.

In situ cancers

For women aged 50–74 during the 2007–2010 period, overdiagnosis from non-progressive cancers accounted for 17.0% (95% CI: 2.5%–35.5%) of all in situ breast cancers diagnosed, whereas the estimate of overdiagnosis due to competitive causes of death was only 1.0% (95% CI: 0.2%–1.7%). When we restricted the analysis to

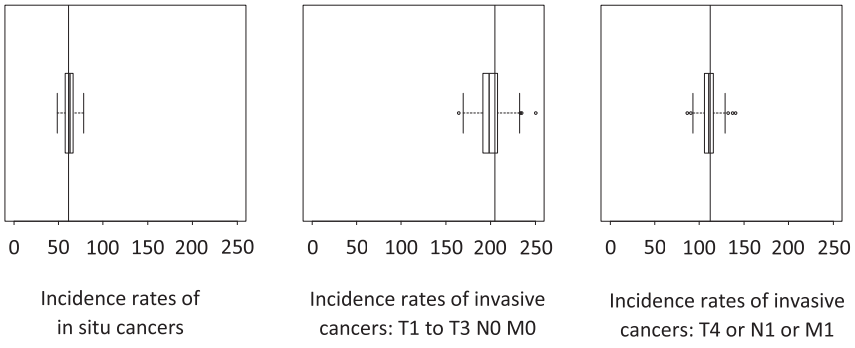

Fig. 2. Distribution of predicted incidence rates of breast cancer for 100,000 women aged 50–74 years, in the Isère Département during the 2007–2010 period. The solid lines show the incidence rates observed. Box plots include median and interquartile range and the whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range from the box.

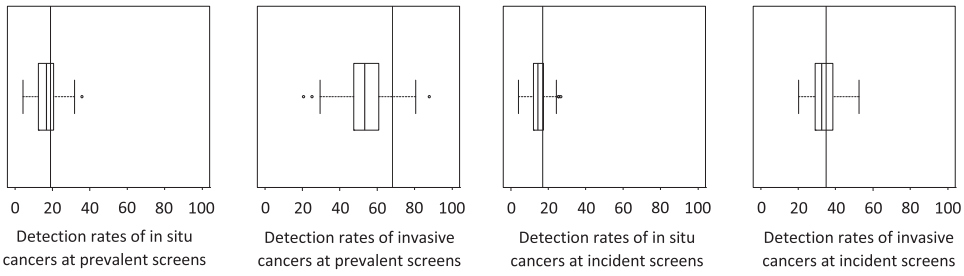

Fig. 3. Distribution of predicted detection rates of breast cancer for 10,000 women aged 50–54 years in the Isère Département during the 2007–2010 period. The solid lines show observed detection rates. Box plots include median and interquartile range, and the whiskers extend to the most extreme data point which is no more than 1.5 times the interquartile range from the box.

Table 1
Median (95% CI) estimates of overdiagnosis associated with breast cancer screening in the Isère Département for women aged 50–74 years during the 2007–2010 period.

	Proportion of overdiagnosis among breast cancers diagnosed		Proportion of overdiagnosis among screen detected breast cancers	
	Due to non-progressive cancers	Due to competitive causes of death	Due to non-progressive cancers	Due to competitive causes of death
In situ	17.0% (2.5%–35.5%)	1.0% (0.2%–1.7%)	20.3% (3.0%–38.9%)	1.3% (0.2%–2.0%)
T1→3N0M0	8.6% (1.2%–15.4%)	0.9% (0.4%–1.3%)	14.1% (2.3%–25.6%)	1.4% (0.8%–2.1%)
T4 |N+| M1	–	1.6% (0.8%–2.6%)	–	15.6% (7.2%–28.4%)
All invasive cancers	5.5% (0.8%–9.8%)	1.1% (0.6%–1.7%)	13.0% (2.2%–23.3%)	2.6% (1.4%–4.0%)

screen detected cancers only, the estimate of overdiagnosis from non-progressive in situ cancers was 20.3% (95% CI: 3.0%–38.9%) and 1.3% (95% CI: 0.2%–2.0%) for overdiagnosis due to competitive causes of death.

Invasive cancers

In the same age group, overdiagnosis from non-progressive cancers was 8.6% (95% CI: 1.2%–15.4%) among early-stage invasive cancers. This estimate of non-progressive cancers accounted for 5.5% (95% CI: 0.8%–9.8%) of all invasive cancers diagnosed. Overdiagnosis due to competitive causes of death was 0.9% (95% CI: 0.4%–1.3%) among early-stage invasive cancers, 1.6% (95% CI: 0.8%–2.6%) among late-stage cancers, resulting in a 1.1% estimate (95% CI: 0.6%–1.7%) among all invasive cancers. Among all screen detected invasive cancers, estimate of overdiagnosis from non-progressive cancers was 13.0% (95% CI: 2.2%–23.3%) and 2.6% (95% CI: 1.4%–4.0%) for overdiagnosis due to competitive causes of deaths. The

Table 2
Types of treatment given for screen detected breast cancers and staged as in situ, T1N0M0, T2N0M0, T3N0M0, in the Isère Département, 2010.

	In situ cancers		Invasive cancers - T1 to T3 N0 M0	
Neoadjuvant chemotherapy	0	0.0%	3	1.4%
Surgery	84	100.0%	217	99.5%
Mastectomy	7	8.3%	18	8.3%
Breast-conserving surgery	76	90.5%	197	90.4%
Unknown	1	1.2%	2	0.9%
2nd-line surgery	16	19.0%	18	8.3%
Lymph node dissection	34	40.5%	214	98.2%
2nd-line lymph node dissection	0	0.0%	2	0.9%
Radiation therapy	55	65.5%	196	89.9%
Chemotherapy	0	0.0%	32	14.7%
Hormone therapy	1	1.2%	170	78.0%
Anti HER2	0	0.0%	8	3.7%
Total	84	100.0%	218	100.0%

Table 3
Median (95% CI) estimates of overtreatment associated with breast cancer screening among women aged 50–74 years in the Isère Département, 2010. Values are expressed for 1000 cancers screened.

	In situ cancers	Invasive cancers	In situ and invasive cancers[a]
Neoadjuvant chemotherapy	0 (0–0)	2 (0–4)	2 (0–3)
Surgery	216 (2–409)	154 (29–276)	171 (30–313)
Mastectomy	18 (3–34)	13 (2–23)	14 (2–26)
Breast-conserving surgery	195 (29–370)	140 (26–250)	155 (27–284)
Unknown	3 (0–5)	1 (0–3)	2 (0–3)
2nd surgery	41 (6–78)	13 (2–23)	21 (3–38)
Lymph node dissection	87 (13–166)	152 (28–272)	134 (24–242)
2nd lymph node dissection	0 (0–0)	1 (0–3)	1 (0–2)
Radiation therapy	141 (21–268)	139 (26–249)	140 (25–254)
Chemotherapy	0 (0–0)	23 (4–41)	16 (3–29)
Hormone therapy	3 (0–5)	121 (23–216)	88 (16–157)
Anti HER2	0 (0–0)	6 (1–10)	4 (1–7)

[a] Distribution of situ and invasive cancers as observed in 2010.

proportion of overdiagnosis due to competitive causes of death among late-stage screen-detected breast cancers was 15.6% (95% CI: 7.2%–28.4%). This result could be explained by the low number of late-stage screen-detected cancers, which resulted in a low value of the denominator used to compute overdiagnosis among screen-detected cancers.

Overtreatment estimates in 2010

The types of treatment that women underwent for the 84 in situ and the 218 early-stage breast cancers detected by individual or organised screening in 2010 are shown in Table 2. The most frequent association of treatments for in situ cancers was surgery and radiation therapy (44%) whereas it was surgery, lymph node dissection, radiation therapy and hormone therapy (60%) for early-stage invasive cancers.

Estimates of overtreatment were computed considering the estimates of overdiagnosis among screen detected cancers, the distribution of in situ and invasive screen-detected cancers in 2010 and treatments realized for these cancers (Table 3). We estimated that among 1000 women with screen-detected breast cancers, 155 (95% CI: 27–284) breast-conserving surgeries, 134 (95% CI: 10–242) lymph node dissections, 140 (95% CI: 25–254) radiation therapies and 88 (95% CI: 16–157) hormone therapies were provided for overdiagnosed cancers.

Discussion

Main results

Among women aged 50–74 during the 2007–2010 period in the Isère Département, overdiagnosis due to non-progressive invasive cancers associated with mammography screening accounted for 5.5% (95% CI: 0.8%–9.8%) of all invasive cancers diagnosed, whereas non-progressive in situ cancers accounted for 17.0% (95% CI: 2.5%–35.5%) of all carcinomas in situ diagnosed. Estimates were 1.0% (95% CI: 0.2%–1.7%) and 1.1% (95% CI: 0.6%–1.7%) for overdiagnosis due to competitive causes of death, for in situ and invasive cancers, respectively. When we restricted the analysis to screen detected cancers, overdiagnosis due to non-progressive cancers was 20.3% (95% CI: 3.0%–38.9%) for in situ and 13.0% (95% CI: 2.2%–23.3%) for invasive cancers, respectively, whereas overdiagnosis due to competitive causes of deaths was 1.3% (95% CI: 0.2%–2.0%) and 2.6% (95% CI: 1.4%–4.0%) for in situ and invasive cancers, respectively.

Finally, estimates of overtreatment involved 171 (95% CI: 30–313) surgeries, 134 (95% CI: 24–242) lymph node dissections, 140 (95% CI: 25–254) radiation therapies and 88 (95% CI: 16–157) hormone therapies for 1000 screen-detected cancers in 2010.

Comparison with previous studies

We previously published an estimate of 1.5% (95% CI: 0.3%–2.9%) for overdiagnosis due to non-progressive invasive breast cancers during the 1991–2006 period in the Isère Département [8]. Two potential reasons might explain this lower estimate for the former period studied. First, the improvement in the mammography technique and the dissemination of digital mammography may have resulted in the detection of smaller cancers more likely to be overdiagnosed in the most recent period. Indeed, an increase of low-intermediate grade ductal carcinomas in situ and small invasive cancers with more favourable tumour characteristics was observed with full-field digital mammography compared with screen-film mammography [14]. Second, we cannot exclude that refinement of our previous simulation model, including the distinction of in situ, early-stage and late-stage invasive cancers, led to changes in estimates. For carcinomas in situ, we obtained a lower median estimate and a narrower credibility interval for the 2007–2010 period, 17.0% (95% CI: 2.5%–35.5%) versus 28.0% (95% CI: 2.2%–59.8%), possibly related to the refinement of the natural history of cancers included in the simulation model.

The independent UK panel on breast cancer screening estimated overdiagnosis by selecting only data from randomised controlled trials with a sufficient follow-up time after the end of invitations [3]. This panel computed an overdiagnosis estimate of 10.7% (95% CI: 9.3%–12.2%) for all in situ and invasive cancers, expressed as a proportion of cancers diagnosed over the whole follow-up period in women invited for screening. This estimate is consistent with our overdiagnosis estimate, which might even be higher if participation rates were more important, as observed in randomized trials. Bleyer et al. estimated that overdiagnosis accounted for 31% of all breast cancers diagnosed using data from the Surveillance, Epidemiology, and End Results to examine incidence trends in the US population [15]. This high estimate might be explained by an inappropriate adjustment for lead time based on the incidence of early- and late-stage cancers [16]. On the other hand, our results are consistent with several studies using observational data. Paci et al. computed a corrected-for-lead-time number of observed cases for each calendar year using an exponential distribution for sojourn times and estimated an excess ratio due to overdiagnosis of 3.2% (95% CI: 1%–6%) in breast cancer screening programmes in Italy [17]. Puliti et al. compared the cumulative incidence of breast cancers in cohorts of attenders and non-attenders followed up several years after the end of invitations and found that overdiagnosis accounted for a 5% increase of invasive cancers [18].

Several authors established an association between the implementation of a screening programme and changes in the types of surgical procedures performed. Paci et al. concluded that the

screening programme was followed by an increase in breast-conserving surgery and a decrease in mastectomies [19]. However, Suhrke et al. concluded that overdiagnosis was likely to have caused an initial increase in surgery rates in the age group screened, including mastectomy, whereas a more recent decline in mastectomy rates affecting all age groups was probably related to changes in surgical policy [5]. Distinguishing the effect of lead time and overdiagnosis on the types of surgery performed is not straightforward with these data. Consequently, the comparison with our estimate of overtreatment was not appropriate.

Balance of benefits versus risks of mammography screening

The median estimates of overdiagnosis showed that the vast majority of screen-detected cancers, i.e. 84% of invasive cancers and 78% of in situ cancers, would have evolved to clinical symptoms and consequently would have been diagnosed in absence of screening. The value of a screening programme is based on the balance of benefits, i.e. reduction in mortality, versus risks including overdiagnosis. Our study was not designed to estimate the mortality reduction associated with screening and consequently we could not directly balance the benefits against the risks of the programme. Balancing our estimate of overdiagnosis against the mortality reduction established in the literature was not possible considering the different types of population used to compute these estimates. Indeed, estimates of mortality reduction are generally obtained in cohorts of women invited to several screening rounds during a long period, whereas our estimate of overdiagnosis was based on cross-sectional data.

Research perspectives include the assessment of the impact of overdiagnosis on mortality and quality of life and the women's point of view on the acceptable ratio of deaths avoided and overdiagnosed cancers.

Strengths and limits

Our approach based on a Bayesian method and population-based data has several strengths. Firstly, we computed an estimate of overdiagnosis adjusted for lead time and for the changes in lifetime risk of breast cancer with successive birth cohorts. Secondly, participation in individual screening was also included in the model since its omission could have resulted in underestimating overdiagnosis [20]. Thirdly, the Bayesian approach made it possible to take into account uncertainties concerning several parameters that could not be assessed precisely, such as the lifetime risk of cancer and participation in individual screening. Prior distributions for these parameters were included in the model instead of making restrictive assumptions. Fourthly, the evolution from in situ to invasive cancers was one of the options included in the natural history of breast cancer, avoiding the implicit assumption of a separate evolution for in situ and invasive cancers. Indeed, the estimation of overdiagnosis among in situ and invasive cancers without taking into account the potential evolution of in situ cancers to invasive cancers may result in overestimating overdiagnosis for in situ cancers as well as underestimating invasive cancers. Finally, the detection rates predicted by the model were close to the detection rates observed in Isère for prevalent and incident screens, even if these rates were not used to calibrate the model. This finding participated in the validation of the model since detection rates depend on age-specific rates of breast cancer, and on the natural history of cancer including the length of pre-clinical phases.

The limitations of our study should be acknowledged. Firstly, even if our model fit data well, we cannot exclude a misspecification of the model, including its natural history. The model assumed five options for the natural history of breast cancers, but the true patterns of how tumours evolve could have been oversimplified. However, the parameters of the distributions used to define the length of the pre-clinical phase for in situ and invasive tumours were estimated using the Bayesian framework to avoid making restrictive assumptions on their values. Secondly, the proportion of prevalent screening rounds was only 30.9% in Isère during the 2007–2010 period and overdiagnosis could be more frequent in a population with higher proportion of prevalent screens. Thirdly, overdiagnosis estimates could be higher in a population with higher participation rates. Fourthly, we used data from the 2007–2010 period and the results obtained may not be extrapolated to more recent periods due to changes in the characteristics of the mammography test with the widespread use of digital mammography and dissemination of tomosynthesis after 2010 [21].

In a systematic review of methods used to estimate overdiagnosis, Carter et al. defined quality criteria for modelling studies [22].

- Extent to which assumptions are transparent and clearly stated; extent to which assumptions are backed by evidence. Supplementary Table 1 described model assumptions as well as their justification and references.
- Probability of bias in the data used by the model. The probability of bias was low since data were obtained from a population-based cancer registry covering a population of 1.2 million inhabitants and its breast cancer screening programme.
- Sensitivity analyses performed for unobservable variables. We realized sensitivity analyses by including the uncertainty in the Bayesian analysis using prior distribution for parameters with unknown values. For example, the uncertainty about participation in individual screening was taken into account through the Bayesian framework by a prior distribution including possible values for this participation rate. Similarly, uncertainty about the natural history of cancers and sojourn times were taken into account using prior distributions to allow different types and lengths of pre-clinical phases. The lifetime risks of non-progressive in situ and invasive cancers were also unobservable parameters that determined the amount of overdiagnosis among all cancers diagnosed. We chose an upper limit of 3% for the prior distribution of the lifetime risk of non-progressive in situ breast cancers. This value resulted in a proportion of non-progressive cancers among all in situ breast cancers diagnosed ranging from 33% to 43%, depending on the lifetime risk of progressive in situ breast cancers. The same value was used for the upper limit of the prior distribution for the lifetime risk of non-progressive invasive cancers assuming that non-progressive invasive cancers could not be more frequent than non-progressive in situ cancers. The proportion of in situ cancers observed in autopsy studies represents an upper limit of the amount of overdiagnosis since some of these in situ cancers would have progressed to clinical symptoms whereas others would also have progressed to invasive cancers. Consequently, the results of autopsy studies could not be directly used to determine the prior distribution of the lifetime risk of non-progressive breast cancer. A review reported a median prevalence of in situ cancers of 8.9% among 7 autopsy studies with wide variations across studies from 0% to 39% [23].
- External validation of the model. Our model was not externally validated. However, a previous version of this model based on a slightly different natural history was used on Isère data from 1991 to 2006 and showed good calibration [8].

Conclusion

Our estimates of overdiagnosis should be balanced against the reduction of breast cancer mortality to assess the value of breast

cancer screening programme. Precise knowledge of the histo-prognostic characteristics associated with slow progressive cancers will help decrease the consequences of overdiagnosis by limiting the treatments dispensed for these cancers.

Ethics

The collection of personal data by the Isère Cancer registry is approved by the Commission Nationale de l'Informatique et des Libertés, which is in charge of ensuring respect for French law on data processing, data files, and individual liberties. The study did not involve experimentation on human subjects and the approval of an ethical committee was not required.

Conflict of interest statement

The authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.breast.2016.04.013.

References

[1] Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev 2011;1:CD001877. http://dx.doi.org/10.1002/14651858.CD001877.pub4.
[2] Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. J Am Med Assoc 2014;311(13):1327–35. http://dx.doi.org/10.1001/jama.2014.1398.
[3] Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. Br J Cancer 2013;108(11):2205–40. http://dx.doi.org/10.1038/bjc.2013.177.
[4] Puliti D, Duffy SW, Miccinesi G, de Koning H, Lynge E, Zappa M, et al. Over-diagnosis in mammographic screening for breast cancer in Europe: a literature review. J Med Screen 2012;19(Suppl. 1):42–56. http://dx.doi.org/10.1258/jms.2012.012082.
[5] Suhrke P, Mæhlen J, Schlichting E, Jørgensen KJ, Gøtzsche PC, Zahl P-H. Effect of mammography screening on surgical treatment for breast cancer in Norway: comparative analysis of cancer registry data. Br Med J 2011;343:d4692.
[6] Paci E, Duffy SW. Overdiagnosis and overtreatment of breast cancer: over-diagnosis and overtreatment in service screening. Breast Cancer Res 2005;7(6):266–70. http://dx.doi.org/10.1186/bcr1339.
[7] Berry DA, Inoue L, Shen Y, Venier J, Cohen D, Bondy M, et al. Modeling the impact of treatment and screening on U.S. breast cancer mortality: a Bayesian approach. J Natl Cancer Inst Monogr 2006;36:30–6. http://dx.doi.org/10.1093/jncimonographs/lgj006.
[8] Seigneurin A, François O, Labarère J, Oudeville P, Monlong J, Colonna M. Overdiagnosis from non-progressive cancer detected by screening mammography: stochastic simulation study with calibration to population based registry data. Br Med J 2011;343:d7017.
[9] Sobin L, Gospodarowics M, Wittekind C. The TNM classification of malignant tumours. 7th ed. 2009.
[10] Bender R, Augustin T, Blettner M. Generating survival times to simulate cox proportional hazards models. Stat Med 2005;24(11):1713–23. http://dx.doi.org/10.1002/sim.2059.
[11] Beaumont MA, Zhang W, Balding DJ. Approximate Bayesian computation in population genetics. Genetics 2002;162(4):2025–35.
[12] Blum MG, François O. Non-linear regression models for approximate Bayesian computation. Stat Comput 2010;20(1):63–73.
[13] Csilléry K, François O, Blum MG. abc: an R package for approximate Bayesian computation (ABC). Methods Ecol Evol 2012;3(3):475–9.
[14] Nederend J, Duijm LEM, Louwman MWJ, Groenewoud JH, Donkers-van Rossum AB, Voogd AC. Impact of transition from analog screening mammography to digital screening mammography on screening outcome in The Netherlands: a population-based study. Ann Oncol Off J Eur Soc Med Oncol ESMO 2012;23(12):3098–103. http://dx.doi.org/10.1093/annonc/mds146.
[15] Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. N Engl J Med 2012;367(21):1998–2005. http://dx.doi.org/10.1056/NEJMoa1206809.
[16] Seigneurin A, Labarère J, Duffy SW, Colonna M. Overdiagnosis associated with breast cancer screening: a simulation study to compare lead-time adjustment methods. Cancer Epidemiol 2015;39(6):1128–35. http://dx.doi.org/10.1016/j.canep.2015.08.013.
[17] Paci E, Miccinesi G, Puliti D, Baldazzi P, De Lisi V, Falcini F, et al. Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy. Breast Cancer Res 2006;8(6):R68. http://dx.doi.org/10.1186/bcr1625.
[18] Puliti D, Miccinesi G, Zappa M, Manneschi G, Crocetti E, Paci E. Balancing harms and benefits of service mammography screening programs: a cohort study. Breast Cancer Res 2012;14(1):R9. http://dx.doi.org/10.1186/bcr3090.
[19] Paci E, Duffy SW, Giorgi D, Zappa M, Crocetti E, Vezzosi V, et al. Are breast cancer screening programmes increasing rates of mastectomy? Observational study. Br Med J 2002;325(7361):418.
[20] Biesheuvel C, Barratt A, Howard K, Houssami N, Irwig L. Effects of study methods and biases on estimates of invasive breast cancer overdetection with mammography screening: a systematic review. Lancet Oncol 2007;8(12):1129–38. http://dx.doi.org/10.1016/S1470-2045(07)70380-7.
[21] Joe BN, Sickles EA. The evolution of breast imaging: past to present. Radiology 2014;273(2 Suppl.):S23–44. http://dx.doi.org/10.1148/radiol.14141233.
[22] Carter JL, Coletti RJ, Harris RP. Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods. Br Med J 2015;350:g7773.
[23] Welch HG, Black WC. Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find? Ann Intern Med 1997;127(11):1023–8.