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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)

2.4.1. Compensatory drop method

Basically, this method assumes that the increase in breast cancer incidence due to lead time in women aged 50–69 years targeted by screening would be fully compensated by a similar decrease in cancers among women aged 70–74 years no longer offered screening, during the year 4 to year 15 period. The formula is as follows:

$$\mathrm{OD}_{50-69} = \frac{(N\mathrm{scr}_{50-69} - N\text{no scr}_{50-69}) - (N\text{no scr}_{70-74} - N\mathrm{scr}_{70-74})}{N\mathrm{scr}_{50-69}} \quad (1)$$

with:

N scr $_{50-69}$: the number of cancers diagnosed in populations aged 50–69 years invited to screening between 50 and 69 years of age with participation rates ranging from 20% to 80%.

N no scr $_{50-69}$: the number of cancers diagnosed in a population aged 50–69 years not invited to screening.

N scr $_{70-74}$: the number of cancers diagnosed in populations aged 70–74 years invited to screening between 50 and 69 years of age with participation rates ranging from 20% to 80%.

N no scr $_{70-74}$: the number of cancers diagnosed in a population aged 70–74 years not invited to screening.

2.4.2. Method based on the incidence of early- and late-stage cancers

This method assumes that an increase in incidence in early-stage cancers due to lead time would be fully compensated by a decrease in late-stage cancers in the same population aged 50–69 during the year 4 to year 15 period.

The formula is as follows:

$$\mathrm{OD} = \frac{(N\mathrm{scr}_{\text{early stage}} - N\text{no scr}_{\text{early stage}}) - (N\text{no scr}_{\text{late stage}} - N\mathrm{scr}_{\text{late stage}})}{N\mathrm{scr}} \quad (2)$$

with:

N scr$_{\text{early stage}}$: the number of early-stage cancers diagnosed in populations invited to screening with a participation rate ranging from 20% to 80%.

N no scr$_{\text{early stage}}$: the number of early-stage cancers diagnosed in a population not invited to screening.

N scr$_{\text{late stage}}$: the number of late-stage cancers diagnosed in populations invited to screening with a participation rate ranging from 20% to 80%.

N no scr$_{\text{late stage}}$: the number of late-stage cancers diagnosed in a population not invited to screening.

We obtained the number of cancers detected in absence of screening from the simulations of populations not invited to screening, since there is considerable disagreement over the appropriate estimation of the risk of cancers in absence of screening.

For each situation, a total of 100 populations were simulated to compute a median overdiagnosis estimate and 95% credibility interval.

3. Results

3.1. Base-case analysis: constant participation rates and lifetime risk of cancer

3.1.1. Overall annual incidence rates

The effect of lead time can be observed at the start of the screening programme at year 0 with a prevalent peak of incidence in a population offered screening (Fig. 1a). From year 4–15, incidence remained higher than in a population not offered screening. Table 2 shows that incidence rates increased with sojourn-time values as well as participation rates.

For individuals aged 50–54 to 65–69 years, a prevalent peak and an increase of incidence several years after the start of the programme were also observed (Fig. 2a–d). A compensatory drop in incidence rates was observed in the 70- to 74-year-old age group because a number of cancers that would have been diagnosed in this age group if no screening programmes were implemented were screen-detected before the age of 70 (Fig. 2e).

3.1.2. Annual incidence rate by stage

In presence of screening, a prevalent peak of incidence was observed for both stages (Fig. 1b). Incidence rates for early-stage cancers remained higher than in a population not offered screening, whereas the incidence of late-stage cancers became lower than in a population not offered screening.

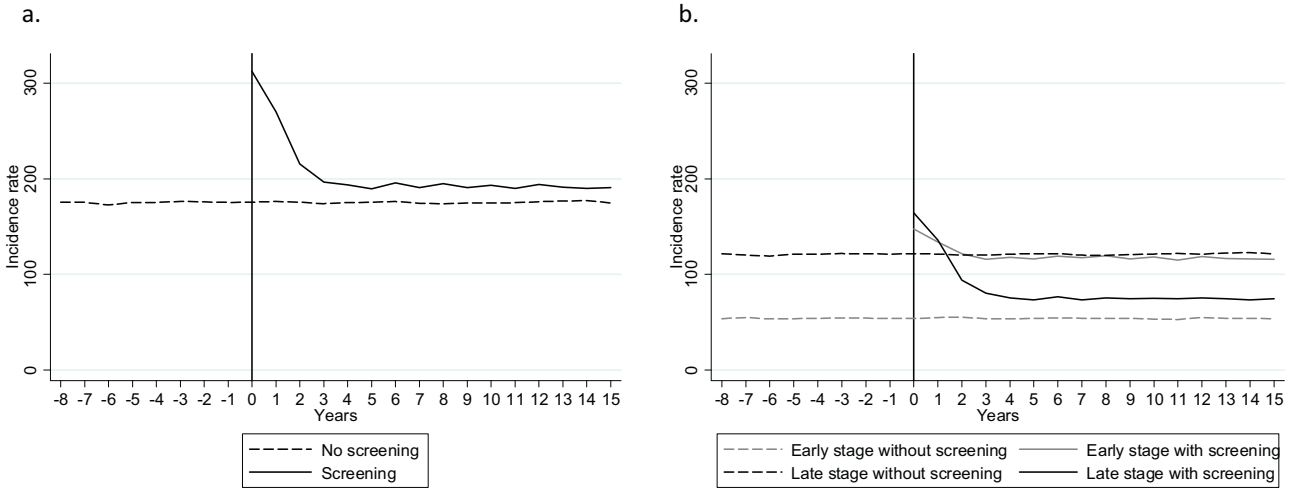

Fig. 1. Simulated overall incidence rates (a) and early-and late-stage incidence rates (b) of breast cancers among women aged 50–69 years experiencing a constant 10% lifetime risk of cancer in a population offered screening from year 0 with a constant 50% participation rates and in a population not offered screening.

Table 2
Simulated Incidence rates per 100,000 for different lifetime risks, participation rates and sojourn times.

Year	Situation 1			Situation 2			Situation 3			Situation 4			Situation 5			Situation 6			Situation 7		
	Risk: 10%			Risk: 10%			Risk: 10%			Risk: 10%			Risk: 10%			Risk: 10–20%			Risk: 10–20%		
	Participation: 0% Sojourn time: 3; 2 / 2			Participation: 50% Sojourn time: 3 ; 2 / 2			Participation: 80% Sojourn time: 3 ; 2 / 2			Participation: 0% Sojourn time: 4.5 ; 3 / 3			Participation: 50% Sojourn time: 4.5 ; 3 / 3			Participation: 0% Sojourn time: 3 ; 2 / 2			Participation: 20–80% Sojourn time: 3 ; 2 / 2		
	In situ	Invasive	Total	In situ	Invasive	Total	In situ	Invasive	Total	In situ	Invasive	Total	In situ	Invasive	Total	In situ	Invasive	Total	In situ	Invasive	Total
0	53.9	121.6	175.5	147.8	164.5	312.2	204.4	189.2	393.6	51.5	111.3	162.8	190.5	177.4	367.8	86.1	194.1	280.2	146.2	220.6	366.8
1	55.1	121.4	176.4	133.8	136.2	270.0	180.9	144.3	324.6	50.0	110.5	160.5	175.3	153.0	328.4	88.0	196.3	284.3	138.6	207.1	345.7
2	55.3	120.2	175.5	121.6	93.9	215.5	161.0	61.8	222.8	51.3	111.0	162.2	148.7	102.7	251.4	89.2	199.9	289.1	160.2	199.1	359.3
3	53.7	120.3	174.1	115.8	80.6	196.4	152.9	50.9	203.7	51.3	111.5	162.8	139.7	89.1	228.8	90.6	202.2	292.8	153.3	181.0	334.3
4	53.7	121.4	175.1	118.1	75.5	193.5	159.4	45.0	204.4	51.3	111.8	163.1	136.0	70.1	206.0	91.8	203.9	295.7	180.9	178.7	359.6
5	53.9	121.5	175.4	116.4	73.2	189.6	153.3	44.5	197.9	51.2	110.9	162.1	132.8	63.3	196.2	91.8	207.5	299.2	175.6	167.1	342.7
6	54.6	121.7	176.3	119.2	76.7	195.9	158.4	45.5	203.9	50.7	111.2	162.0	136.3	60.7	197.0	93.3	208.3	301.6	207.8	167.2	375.0
7	54.2	120.2	174.4	117.4	73.6	190.9	152.1	45.5	197.6	50.7	111.4	162.1	133.2	60.4	193.6	94.5	209.5	304.0	199.1	157.7	356.7
8	53.9	120.0	173.9	119.8	75.3	195.1	158.3	45.6	203.9	50.6	111.9	162.5	135.1	61.2	196.3	95.3	212.2	307.5	229.7	156.7	386.4
9	54.0	120.7	174.6	116.2	74.6	190.8	154.1	45.4	199.5	51.6	110.3	161.9	134.9	60.9	195.8	95.3	214.3	309.6	223.2	146.7	370.0
10	53.3	121.4	174.7	118.3	75.0	193.3	158.8	45.6	204.4	51.9	110.7	162.6	137.7	60.4	198.1	97.5	220.9	318.4	252.8	141.4	394.2
11	53.0	122.0	175.0	115.0	74.9	189.9	153.9	44.8	198.8	50.8	111.1	161.9	131.7	60.3	192.0	98.5	219.8	318.3	246.5	132.0	378.5
12	54.9	121.3	176.2	118.9	75.4	194.3	160.4	46.0	206.4	50.1	111.3	161.4	136.7	61.7	198.4	100.4	222.8	323.2	281.4	127.4	408.8
13	54.2	122.5	176.7	116.7	74.6	191.3	152.8	44.4	197.2	51.6	112.1	163.7	132.6	61.9	194.5	100.9	226.5	327.4	270.8	118.8	389.6
14	54.2	123.0	177.3	116.5	73.6	190.1	154.3	43.6	197.9	51.0	111.4	162.4	132.0	59.6	191.6	100.1	228.5	328.6	295.6	108.4	404.0
15	53.5	121.4	174.9	116.0	74.8	190.9	153.7	46.3	200.0	51.5	112.5	164.0	134.7	60.5	195.1	101.9	230.6	332.5	298.7	107.9	406.6

3.1.3. Overdiagnosis

The overdiagnosis estimate based on the compensatory drop in incidence among individuals aged 70–74 years was −0.1% (95% CI, −0.5% to 0.5%) with 50% participation rates in screening from year 0 to 15 (situation 2).

In the same situation, the estimate of overdiagnosis using the incidence of early- and late-stage cancers to adjust for lead time was 8.9% (95% CI, 8.5–9.3%) during the period between years 4 and 15.

3.2. Sensitivity analysis: increasing participation rates and lifetime risks of cancer

3.2.1. Overall annual incidence rates

Simulations were carried out for an increase in the lifetime risk of cancer from 10% to 20% between the 1900 and 1950 birth cohorts, and an increase in the participation rate in screening from 20% at year 0 to 80% at year 15 (situation 7).

Fifteen years after the start of the screening programme, incidence rates among women aged 50–69 remained higher than in a population not offered screening (Fig. 3a and Table 2).

Similar findings were found for all 5-year age groups (Fig. 4a–e). For individuals aged 70–74 years, incidence rates were lower in presence of screening and the difference in incidence for screened and unscreened populations increased with calendar years.

Prevalent peaks of incidence were observed for early- and late-stage cancers (Fig. 3b). The incidence of early-stage cancers remained higher in a population offered screening than in a population not offered screening and increased with calendar year, whereas the incidence of late-stage cancers rapidly lowered in a population offered screening.

Figs. 1 and 3b show that the incidence of late-stage cancers is lower in a population of women invited to screening. These findings are worth emphasizing as they indicate a potential benefit of screening for a part of the population with a protection against advanced cancers that are the most difficult to treat.

3.2.2. Overdiagnosis

The estimate of overdiagnosis using the compensatory drop method was 11.0% (95% CI, 10.5–11.6%) during the year 4 to year 15 period, whereas the method based on the incidence of early- and late-stage cancer provided an estimate of 17.6% (95% CI, 17.4–17.9%) for overdiagnosis.

4. Discussion

We used simulated data to assess the accuracy of two lead-time adjustment methods to estimate overdiagnosis with annual incidence rates. These results highlight that the method based on the compensatory drop of incidence provided an accurate adjustment for lead time and consequently an unbiased estimate of overdiagnosis in the particular situation of constant participation rates and lifetime risk of cancers. However, if participation rates in screening increased with calendar year as well as lifetime risk of cancer with birth cohorts, this method overestimated overdiagnosis. The method based on the incidence of early- and late-stage cancers overestimated the amount of overdiagnosis in both situations regarding lifetime risk of cancer and participation rates, suggesting an inappropriate adjustment for lead time.

The compensatory drop method adjusts correctly for lead time when using incidence computed by birth cohort. In this case, an increase in incidence in the age group targeted by screening will be compensated for by a decrease in incidence when individuals are no longer invited to screening. With annual incidence rates, i.e. cross-sectional data, individuals invited to screening and those no longer invited are compared during the same period but do not

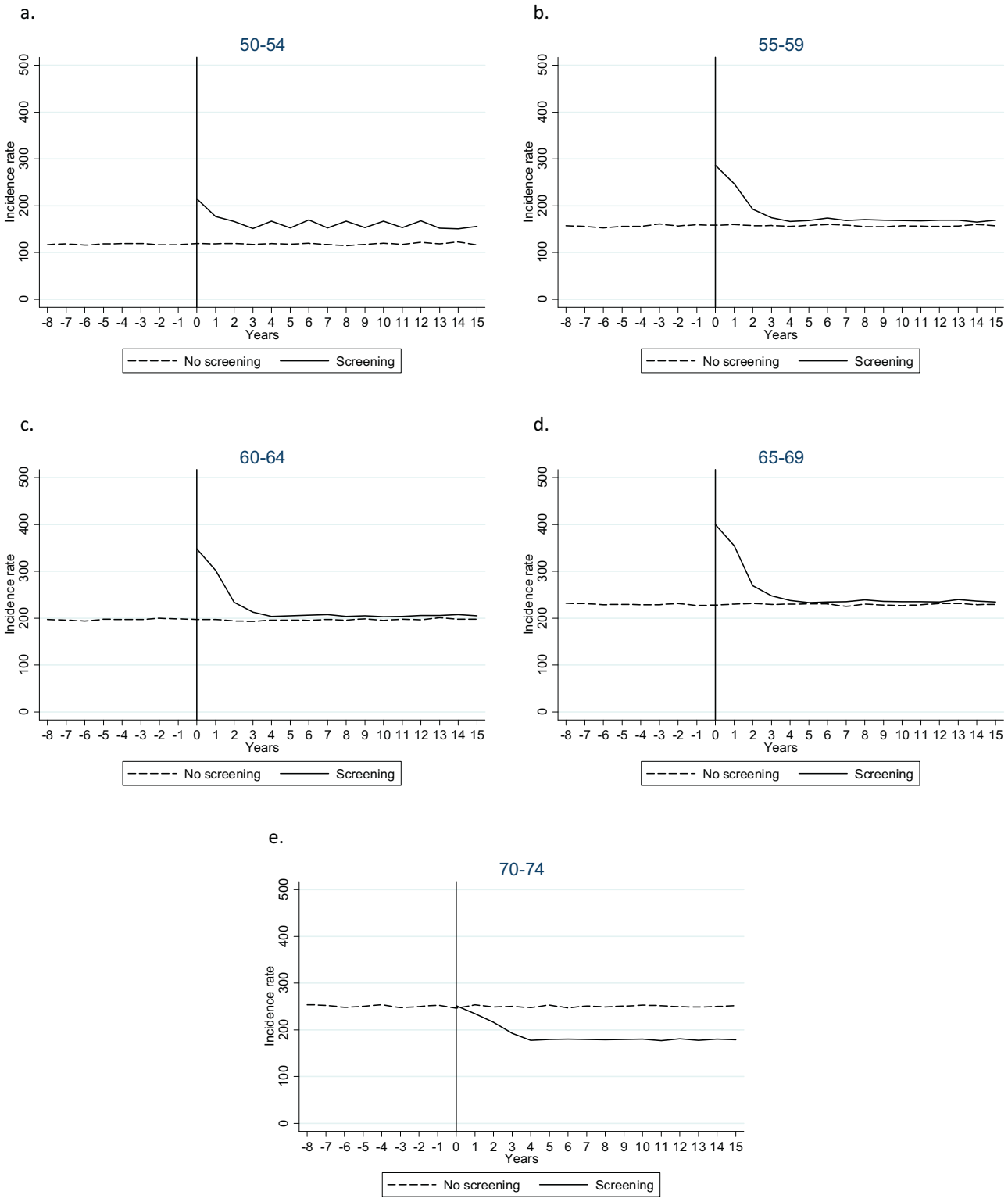

Fig. 2. Simulated age-specific incidence rates of breast cancers among women aged 50–54 (a), 55–59 (b), 60–64 (c), 65–69 (d) and 70–74 (e) years experiencing a constant 10% lifetime risk of cancer in a population offered screening from year 0 with a constant 50% participation rates and in a population not offered screening.

come from same birth cohorts. Therefore, the adjustment for lead time is correct only in a steady-state situation concerning lifetime risks and participation in screening. In case of increasing risk of cancer for successive birth cohorts, the computation of a compensatory drop using annual incidence rates observed during the same period resulted in an inadequate adjustment for lead time due to the anticipation of the temporal trend.

The lead-time adjustment method based on early- and late-stage cancer resulted in an overestimate of overdiagnosis. Lead time implies that some cancers that would have been detected at

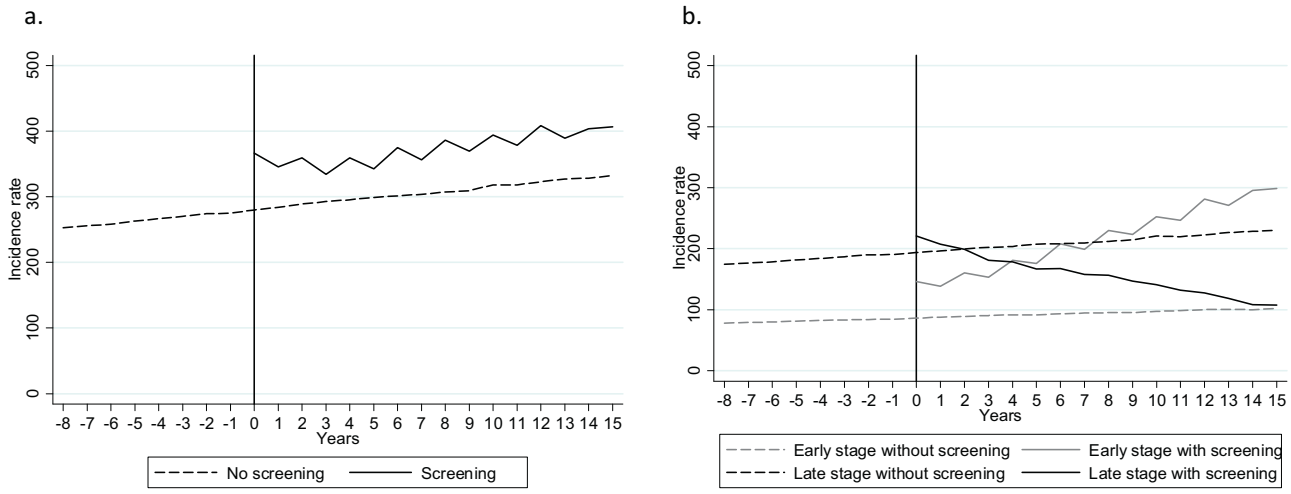

Fig. 3. Simulated overall incidence rates (a) and early- and late-stage rates (b) of breast cancers among women aged 50–69 years experiencing an increase of the lifetime risk of breast cancer from 10% for 1900 birth cohort to 20% for 1950 birth cohort in a population offered screening from year 0 with an increasing participation rates from 20% at year 0–80% at year 15, and in a population not offered screening.

the late stage without screening are diagnosed at an earlier stage in a screening setting. Consequently, a decrease in incidence of late-stage cancers reflects lead time. However, our results showed that the effect of lead time was not accounted for entirely with this method. The main explanation for this inadequate adjustment comes from the use of cross-sectional data instead of cohort data, with an increase in incidence observed each calendar year as individuals reach the lower age limit of the screening programme [15]. Moreover, a sufficient time after the end of the invitations should be included to fully compensate the increase in early-stage cancer incidence with a decrease in late-stage cancer incidence.

These findings have direct implications for the assessment of the accuracy of published estimates of overdiagnosis. Bleyer and Welch used data from cancer registries to examine trends from 1976 through 2008 in the incidence of early-stage breast cancer (ductal carcinoma in situ and localized disease) and late-stage breast cancer (regional and distant disease) among women 40 years of age or older [12]. They first computed the underlying incidence without screening using projections from a pre-screening period. Then they corrected the increase in early-stage cancer diagnosis with the reduction in late-stage cancer diagnosis to adjust for lead time. Their estimates of overdiagnosis among all breast cancers diagnosed were 31%, 26% and 22%, depending on the assumptions about underlying incidence. They concluded that concerns about lead time were eliminated because their study covered 33 years and sufficient time was considered for the surplus of diagnoses of early-stage cancer to translate into a reduction in diagnoses of late-stage cancer. Yet our findings suggest that overdiagnosis might be overestimated due to an inadequate adjustment for lead time when using cross-sectional data instead of cohort data.

Jørgensen and Gøtzsche estimated the extent of overdiagnosis using data on incidence trends in several countries [11]. They computed overdiagnosis after adjusting for the compensatory drop observed the same year in the age group too old to be screened. Their estimates were 44%, 46% and 52% for invasive and in situ cancers in Canada, Sweden and Norway (AORH counties), respectively. Overdiagnosis might have been overestimated in this study since the risk of cancer probably increased with time, as suggested by the increasing trends in incidence observed among women too young to be screened during the pre-screening period. Indeed, our results show that the compensatory drop method yields accurate estimates of overdiagnosis only when the risk of cancer remains constant with time.

Our results highlight the changes in incidence rates of early- and late-stage cancers in a population offered screening, resulting from the detection by screening of early-stage cancers that would have been diagnosed at late stage when clinical signs occurred. Considering that in situ cancers may evolve to invasive cancers, this result emphasises the potential bias when computing an overdiagnosis estimate based on incidence rates of in situ and invasive cancers without taking into account the potential evolution of in situ to invasive cancers.

The strengths of our study include the use of simulated data to control the amount of overdiagnosis and the lifetime risk of cancer for each birth cohort. Consequently, we could illustrate the effect of screening on incidence rates attributable to lead time and highlight the corrections required when estimating overdiagnosis. We also pointed out the potential impact of the increasing lifetime risk of cancers as well as changes in participation rates in screening over the study period.

The limitations of our study should be acknowledged. First, our assumptions regarding sojourn times and participation rates in screening likely oversimplify the actual situation. Values for sojourn times are not precisely known and consequently adjustments required for lead time may not be straightforward in real life. For example, the compensatory drop method calculates the incidence in the age group above the target age group for screening. The computation of an estimate of overdiagnosis accurately adjusted for lead time implies defining a range for this age group greater than the sojourn-time values of all screen-detected cancers. Indeed, if a cancer screened at the beginning of its pre-clinical phase at 69 years is diagnosed at 76 years without screening, a decrease in incidence would not be observed among women aged 70–74 years. Moreover, individuals older than the upper age limit for participation in screening can benefit from individual screening. In this case, the adjustment for lead time would be inaccurate and the estimates of overdiagnosis biased. Finally, we did not tackle the important issue of the method used to estimate the incidence that would have been observed without screening.

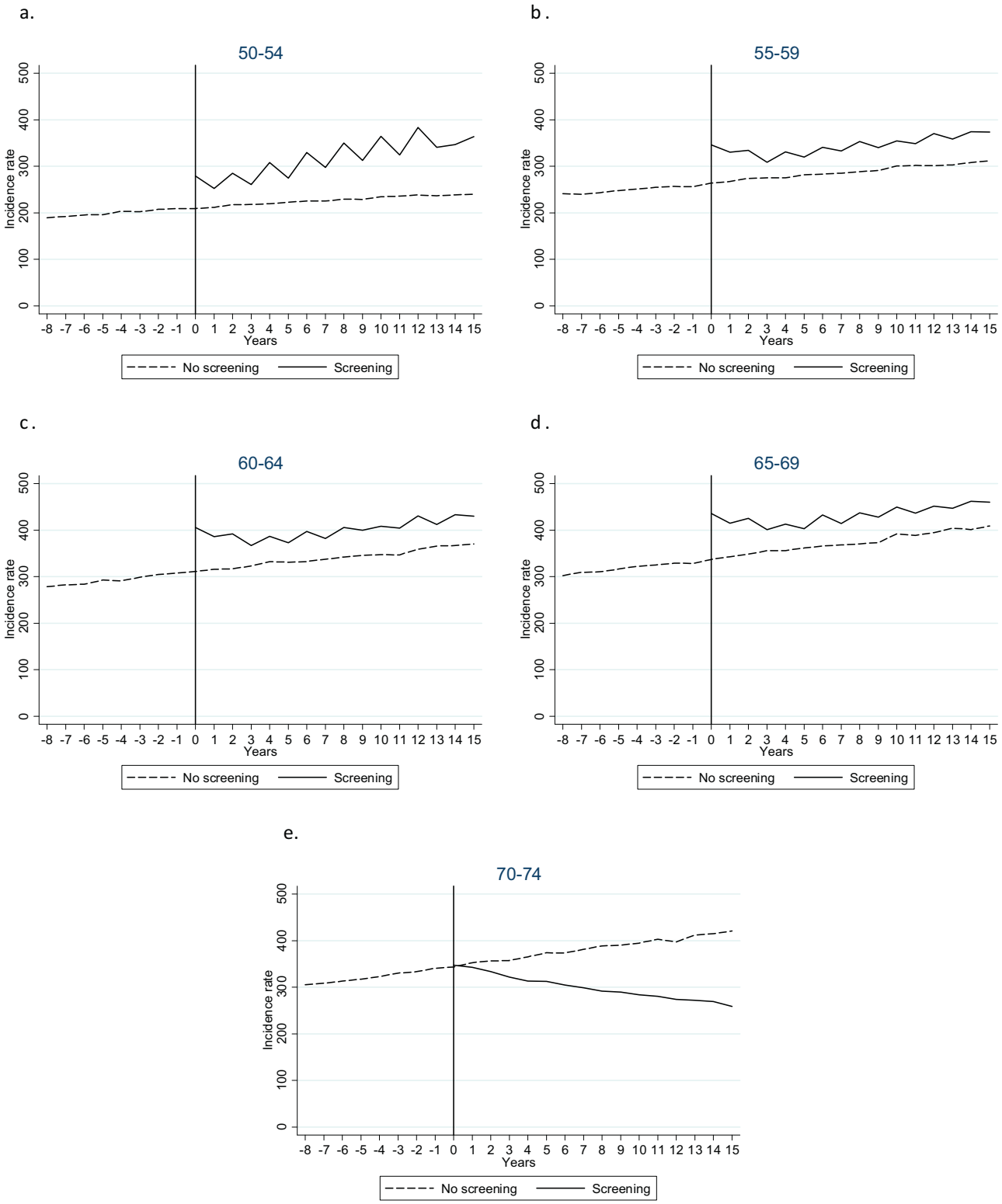

Fig. 4. Simulated age-specific incidence rates of breast cancers among women aged 50–54 (a), 55–59 (b), 60–64 (c), 65–69 (d) and 70–74 (e) years experiencing an increasing lifetime risk of cancer from 10% for 1900 birth cohort to 20% for 1950 birth cohort, in a population offered screening from year 0 with an increasing participation rates from 20% at year 0–80% at year 15 and in a population not offered screening.

5. Conclusion

Because of their availability, the use of annual incidence rates from population-based cancer registries is useful to estimate overdiagnosis associated with a cancer screening programme. However, an accurate adjustment for lead time is necessary to obtain an unbiased estimate of overdiagnosis. The compensatory drop method provides accurate estimates when the lifetime risk of cancer and participation rates remain constant with time but overestimates overdiagnosis in case of increasing risk of cancer and

participation rates with time. The method based on the incidence of early- and late-stage cancers overestimates overdiagnosis due to an inaccurate adjustment for lead time.

Authors contributions

The authors contributions were as follows: Arnaud Seigneurin had the idea for the study, developed the study protocol, obtained funding, analyzed the data, and drafted, revised and submitted the manuscript. José Labarère, Stephen Duffy and Marc Colonna supervised the analysis of data and reviewed the manuscript.

Conflicts of interest

None declared.

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