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The estimations of overdiagnosis in breast cancer screening vary between 0% and over 50%: why?

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Abstract

Background

Published estimations of the extent of breast cancer overdiagnosis vary widely, and there have been heated debates around these estimations. Some high estimates have even been the basis of campaigns against national breast cancer screening programs. Identifying some of the sources of heterogeneity between different estimates would help to clarify the issue.

Methods

The simple case of neuroblastoma - a childhood cancer - screening is used to describe the basic principle of overdiagnosis estimation. The more complicated mechanism of breast cancer overdiagnosis is described based on data from Denmark.

Findings

Analysis of the data from Denmark demonstrates the importance of using individual patients' data and identifies the use of aggregated data as the main reason for overestimation of overdiagnosis.

Interpretation

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3 Many estimates of overdiagnosis associated with breast cancer screening programs
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5 are serious overestimations.
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1. Introduction

Many countries have a national breast cancer screening program in which all women belonging to a specific age-group are invited to have regular mammograms. These programs have been criticized, with claims that their benefit has been overestimated and that the risk of overdiagnosis has been understated. Here, overdiagnosis is defined as the diagnosis, by a screening procedure, of a cancer that would never have become symptomatic during the life of the person.

Both in situ and invasive cancers will be included in the estimation of overdiagnosis, since an overdiagnosed in situ breast cancer leads to an unnecessary treatment, which can include a mastectomy, a reconstructive surgery, and a cosmetic surgery on the other breast to restore symmetry.

The estimations of overdiagnosis in breast cancer screening vary between 0% and more than 50% (Figure 1), and the variety of these estimations contributes to the vigorous debate on the usefulness of breast cancer screening programs[1]. Since it is extremely unlikely that overdiagnosis varies to such a large extent from one program to another, one needs to study possible causes for this observed heterogeneity.

2. Screening for neuroblastoma

We shall start by introducing some basic concepts about screening diagnosis, using the example of the screening for neuroblastoma, a paediatric cancer of neuroblasts (specialized nerve cells). The screening test is a measurement of urinary catecholamines, which are hormones produced by neuroblastoma cells. A study conducted in Germany compared the incidence of neuroblastoma in regions without screening and in experimental regions where screening of one-year-old children was systematically offered [2].

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3 Such a screening program causes an increased incidence of cases immediately after
4 screening (age 1 for neuroblastoma), a decrease shortly afterwards, and a return to
5 normal thereafter (around age 5 for neuroblastoma) (Figure 2a) [3]. In theory, the
6 screening program should allow the detection of the same number of cases, only
7 earlier (Figure 2b). Therefore, if there is no overdiagnosis, the number of cases
8 additionally diagnosed during screening (solid green) is equal to the number of cases
9 that would have been diagnosed later, if there was no screening. Thus,
10 overdiagnosis is measured by the difference between these two numbers (Figure 2c).
11 In the German study, there were 7.3 and 14.2 cases per 100,000 children,
12 respectively, in the control and experimental regions (Figure 2d). Overdiagnosis is
13 the difference between these cumulative incidences, generally expressed as a
14 percentage. Here, it represented 49% $[(14.2-7.3)/14.2]$ of the cases found in the
15 population invited to screening.
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33 This simple example shows the importance of the follow-up duration in correctly
34 estimating the amount of overdiagnosis. In the most extreme case, one would
35 compare the incidences observed at one year of age only, which would then attribute
36 overdiagnosis to all cases with a diagnosis brought forward by screening. Figure 2b
37 shows that the incidence of neuroblastoma at age 5 and over is again the same in
38 the two populations, which is why overdiagnosis has been estimated by comparing
39 the cumulative incidence with and without screening between 12 and 60 months of
40 age (Figure 2d, based on reference [2]).
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51 This study showed that screening for neuroblastoma at one year of age identified
52 many cases that would have regressed spontaneously. In the end, almost half of the
53 diagnoses were unnecessary and and detrimental to the child and his/her family;
54 therefore, this screening is no longer offered.
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3. Breast cancer screening: example of the Funen data

The estimation of overdiagnosis

To evaluate the amount of screening-induced overdiagnosis in breast cancer, we shall use data from Denmark, as studied by Njor et al. [4]. The data used were individual data, i.e., for each woman, her date of birth, history of mammography, and, where applicable, dates of breast cancer diagnosis and death.

This type of screening is a very different situation: in breast cancer screening programs, the same woman may be invited several times, at different ages, whereas children in the neuroblastoma study were all screened only once at 12 months old. Thus, while age was sufficient to evaluate overdiagnosis in neuroblastoma, one needs to take both age and calendar time into account to understand overdiagnosis in breast cancer, which adds a layer of complexity. This breast cancer study measured overdiagnosis by comparing the incidence of breast cancer in several places in Denmark (Funen Island, where there was a screening program, versus other regions, where there was not) and during several periods (at the time of the screening program versus beforehand).

To describe the screening experience of a population over time, a Lexis diagram is often used. An example is presented in Figure 3a: the horizontal axis represents the calendar time, and the vertical axis represents the age of the person. Thus, the trajectory of a given woman is a diagonal, starting at age 0 on her date of birth. A generation can therefore be represented by a parallelogram. In Funen Island, the screening program started on November 1, 1993, and the whole female population aged 50 to 69 was invited.

Each screening round lasted two years; therefore, the first round spanned from November 1, 1993 to October 31, 1995. During the first three rounds, women were

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3 invited again, even if they were over age 70. Figure 3b shows the study inclusion
4 design on a Lexis diagram. The study followed all patients from screening start until
5 31/12/2009 at the latest. Therefore, in order to have sufficient follow-up time, Njor et
6 al. included only patients aged 59 to 70 on November 1, 1993, as younger patients
7 would not have been followed for long enough [4]. In the figure, the intersection of the
8 “study duration” area, the “screening age span” area, and the “included women” area
9 identifies the screened population during screening (yellow) and during follow-up
10 (grey).
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21 Since Funen was not the experimental arm of a randomized trial, there was no
22 obvious control population allowing direct estimation of overdiagnosis. Thus, to
23 evaluate the extent of overdiagnosis, one needs to estimate the incidence expected
24 in Funen without screening.
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30 Two types of potential control populations can be considered: 1) the population of a
31 region without screening at the time when screening was offered in the experimental
32 region, allowing a comparison between “here with screening” and “elsewhere without
33 screening”, and 2) the population in the experimental region before screening,
34 allowing a comparison between “before without screening” and “after with screening”.
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40 In the study of Funen, the control data available were data from Danish regions
41 without screening at the time of screening in Funen (generation November 1, 1923-
42 October 31, 1934), data from Funen before screening (generation November 1,
43 1912-October 31, 1923), and data from Danish regions without screening before the
44 introduction of screening in Funen (generation November 1, 1912-October 31, 1923).
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53 Figure 3c is the Lexis diagram of the study period for women aged 60 and higher,
54 representing a comparison of the studied screened population (S, generation 1923-
55 1934) to the local historical control population (H, generation 1912-1923). Njor et al.
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3 identified five periods of observation in the screened population: the first screening
4 round (prevalence screening), the later screening rounds (incidence screening),
5 which included women aged 70+ for the first three rounds, and three periods
6 corresponding to follow-up 0 to 3 years, 4 to 7 years, and 8+ years from the end of
7 invitation to screening, respectively [4]. By comparing each period of observation to
8 its historical situation, it is possible to estimate the number of cases that would have
9 been diagnosed in Funen if there was no screening program. However, this is still
10 only half of the solution, as it would not take into account the effect of geography.
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Simplified presentation of overdiagnosis estimation in Funen

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23 To understand the estimation of the breast cancer incidence that would be expected
24 if screening did not occur in Funen at the time of screening, let's focus on two one-
25 year generations: 1) women born in 1922 who were 71 on 1/11/1993 and, hence,
26 were never invited to screening; and 2) women born in 1932 who were 61 on
27 1/11/1993 and, hence, were invited to screening.
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35 Table 1 and the corresponding Figure 4 show the incidence as a function of age in
36 these two generations, in Funen versus in other regions. Before screening (1922
37 generation), the incidence was rather similar in Funen (dashed red line) and in other
38 regions (dashed black line), the data being more erratic in Funen due to its
39 population being eight times lower than in the other regions. In the other regions,
40 where there was no screening, the breast cancer incidence increased at all ages
41 between the 1922 generation (black dashed line) and the 1932 generation (black
42 solid line). This can be explained by the improvement in imaging and diagnostic
43 techniques, among other things, during these 10 years.
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55 Therefore, a simple estimation of the incidence that would be expected in Funen if
56 there was no screening in the 1932 generation can be obtained by applying this
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3 estimation of the effect of time to the incidence observed in Funen in the 1922
4 generation. In practice, this is done by increasing the incidence observed in Funen in
5 the 1922 generation, or a smoothed version of it, by the linear increase observed in
6 the other regions. This is a partial view of the data from Denmark, which is shown
7 here just to illustrate the principle of the method. Using the totals in Table 1 would
8 lead to a ratio of cumulative incidences equal to $1.03 [(1436 \times 1065) / (1082 \times 1371)]$;
9 hence, giving a 3% estimation of overdiagnosis.
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19 **Overdiagnosis estimation in Funen**

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21 The analysis by Njor et al. is actually more complete and relies on a mathematical
22 model including screening invitation (yes/no), period (before/after screening), region
23 (other/Funen), and generations, along with interactions between periods and
24 generations [4].
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30 As described in Table 2 and the corresponding Figure 5, this model allows an
31 estimation of the incidence of breast cancer in Funen in the case where there was no
32 screening program, taking into account all the above-mentioned factors. It is then
33 possible to compare the incidence of breast cancer in both populations, separately in
34 each generation. By analogy, this is the equivalent of Figure 2d, for which it was
35 possible to place the age directly on the x-axis, as the screening was performed at
36 the same age for everyone.
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46 This leads to an estimation of overdiagnosis of 1%, based on the data observed in
47 Funen, addressing possible differences in the incidence between periods, between
48 Funen and the other regions, and between generations, as well as possible
49 interactions.
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55 In their article, Njor et al. also present a 5% estimation based on the data observed in
56 Copenhagen, where screening started on January 1, 1991, and concluded with a
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3 global estimation of 4% overdiagnosis, based on all the data available in Denmark
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5 [4].
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8 **4. Analysis of aggregated data**

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10 The data presented by Njor et al. are individual data, allowing the follow-up of each
11 woman, invited to screening or not, residing in Funen or in another region, including
12 the relevant dates (of birth, of screening invitation, of actual screening, of diagnosis,
13 and of death) [4].
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19 However, a large number of overdiagnosis estimations rely on aggregated data.
20 These aggregated data are incidences observed by periods and by age-groups,
21 which are publicly available for breast cancer in many countries, hence the popularity
22 of their analysis.
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28 To understand the difference between aggregated and individual data, the Lexis
29 diagram is again useful. Jørgensen et al. estimated breast cancer overdiagnosis in
30 Denmark using aggregated data from two periods, 1971-1990 (without screening)
31 and 1991-2003 (with screening) in two age-groups: 50 to 69 and 70 to 79 [5].
32 Therefore, these four populations are represented by four rectangles in the Lexis
33 diagram (Figure 6), instead of parallelograms corresponding to the follow-up of
34 generations.
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44 Jørgensen et al. first estimated the relative risk of breast cancer in the 50 to 69 age
45 group during the screening period (solid orange rectangle) as compared to the risk in
46 the same age group during the reference period (faded orange rectangle) [5]. They
47 used this relative risk to estimate the initial excess of cases, due to screening. They
48 then estimated the same relative risk in the 70-79 age group (solid and faded yellow
49 rectangles), and used it to estimate the post-screening deficit, the number of cases
50 that would have been diagnosed later if there was no screening. By subtracting the
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3 post-screening deficit from the initial excess, they estimated the number of “falsely”
4 diagnosed breast cancers, which was translated to a 33% rate of overdiagnosis.
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7 Two major flaws with this design are shown on Figure 6. The first is that a fraction of
8 the patients, shown in the upper yellow triangle, were never screened, because they
9 were older than the upper age-limit for screening at the beginning of the screening
10 period. The inclusion of these unscreened older patients in the “post-screening”
11 follow-up overestimates the overdiagnosis rate. The second flaw is that the screened
12 patients in the lower orange trapezoid were never followed up, so there is no
13 information on a possible compensatory drop in later incidence. Moreover, this
14 design cannot adjust for the evolution of medical techniques and imaging over time.
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28 **5. Discussion**

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30 Another paper by Njor et al. reviewed five of the most quoted studies, which had
31 produced high estimates of overdiagnosis (some of these studies considered only
32 invasive breast cancers) [6–11]. The data and the method used in each of these
33 studies were identified, and each method was then applied to data from Denmark,
34 adapting the timing to correspond to the timing of screening in Funen. Njor et al.’s
35 2018 study shows that using these methods leads to mistakenly high estimates of
36 overdiagnosis, explained essentially by a too short duration of follow-up and by an
37 inadequate estimation of the incidence expected without screening in the population
38 invited to screening [6].
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51 **Follow-up duration**

52 The first problem is a too short follow-up duration in the populations that are being
53 compared. Similar to the neuroblastoma example, if one wants to compare the
54 number of breast cancers in a screened and an unscreened population, the two
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3 populations must be followed-up long enough after the end of screening to avoid
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5 attributing the excess incidence observed by the screening to overdiagnosis.
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8 Zahl et al., for instance, studied the incidence in a population invited to screening
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10 only during the first five years of the program (1996-2000), and could not measure
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12 the complete post-screening deficit [7]. They assumed it to be negligible based on
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14 the trend in breast cancer incidence in the population aged 70 or over. However, it is
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16 not the largely unscreened population aged 70 and over who should be considered:
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18 what is needed is the breast cancer incidence in the screened population at age 70
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20 or over. Zahl et al. attributed the total excess incidence in the screened group to
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22 overdiagnosis, without taking into account the diagnoses brought forward by
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24 screening and therefore unobserved later. This explains the mistakenly high estimate
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26 of overdiagnosis.
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30 **The incidence expected in the absence of screening**

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33 In this case, where there are no data from randomized trials, one needs to estimate
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35 the breast cancer incidence that would be expected without screening in the
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37 population invited to screening. This is generally estimated on the basis of the
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39 observed incidence at the same time in an unscreened population geographically
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41 close to the population invited to screening, or in the population invited to screening
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43 before the start of the screening program. This requires some assumptions on the
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45 variation in breast cancer incidence with space and with time. The validity of the
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47 estimation depends on the validity of these assumptions.
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51 Jørgensen and Gotzsche estimated the expected incidence without screening by
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53 linearly extrapolating the pre-screening incidence and concluded that there was 30%
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55 to 40% overdiagnosis in Funen [9]. The same linear extrapolation performed in
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57 regions without screening would lead to an increase in the expected incidence
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3 between 12% and 17%. They have therefore attributed part of the increase, which
4 was unrelated to screening but simply the effect of time, to overdiagnosis.
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7 Similarly, Zahl and Maehlen assumed the breast cancer incidence to have remained
8 stable in Norway before and during screening, but the national registry data show
9 that, in Norway just like in Denmark, breast cancer incidence was on the increase
10 before screening started [10]. Taking this increasing trend into account reduces the
11 estimation of overdiagnosis from 42% to 13%.
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19 **6. Conclusion**

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21 These analyses show empirically the diversity of estimations that can be obtained on
22 the basis of the same data, using different methods. The estimations vary between
23 0% and 55%, but some rely on data observed on the same women; hence, they
24 cannot all be correct.
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30 An important difference between studies is the use of individual versus aggregated
31 data. Figure 1 shows that all the studies providing estimates above 17% were based
32 on aggregated data; conversely, none of the studies based on individual data
33 provided estimates above 17%. However, some studies of aggregated data obtain
34 estimations below 17%; some of these use the simulation program MISCAN and
35 others were done by the Euroscreen working group.
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44 In conclusion, the estimation of overdiagnosis is a difficult exercise. The analysis of
45 individual data is generally less biased. The screened population must be followed-
46 up for several years after the end of screening, and the adequacy of the estimated
47 incidence expected without screening in the screened population must be discussed.
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49 The exposure of the population to different breast cancer risk factors (age at first
50 pregnancy, number of children, alcohol consumption, and hormonal treatment for
51 menopause...) may have varied with time, and some of these factors have different
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3 effects according to age. Some exposures may also vary with area. For instance, a
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5 reduced use of hormonal treatment for menopause over time will lead to a reduction
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7 in the incidence of post-menopausal breast cancer only, and the use of hormonal
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9 treatment for menopause may have been reduced earlier in some parts of a country
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11 than in others.
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14 In the end, any overdiagnosis estimation is an arithmetic combination of observed
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16 data. The selection of the data and the way to combine them are more or less
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18 judicious, depending on what the investigators have understood of the problem.
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Statements

Contributorship

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26 Both DC and CH were involved in the conceptualisation of the overall paper and
27
28 successive drafts, and contributed to the planning, conduct, and reporting of the work
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30 described in the article. CH was responsible of the design of the paper.
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Competing interests

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35
36
37 There are no competing interests for any author
38

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40
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42
43 Roussy, the largest cancer hospital in France, and CH has retired from the same
44
45 Institute.
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Tables

Table 1: Breast cancer incidence per 100,000 by age-group in Funen and in other regions for two generations, taken from Fig. 2 of Njor et al. 2018 [6].

Age-group	Other regions, generation 1922	Other regions, generation 1932	Funen, generation 1922	Funen, generation 1932
			(without screening)	(with screening)
50-54	153	181	166	210
55-59	178	216	152	202
60-65	204	281	236	402
65-69	237	325	251	373
70-74	293	368	278	249
Total	1065	1371	1083	1436

Table 2: Breast cancer incidence per 100,000 observed in Funen for every generation, and model estimations in the case of no screening program. Adapted from Njor et al. 2013 [4].

Period	Before screening	Invitation to screening		Follow-up post-screening			Cumulative over generations
		1st	Further	0-3 years	4-7 years	8+ years	
		screen	screens	after	after	after	
Observed	260	659	402	260	340	453	392
Expected*	260	358	352	388	411	462	387
RR	1.00	1.84	1.14	0.66	0.82	0.97	1.01

* The expected case number is calculated from model estimations, which take into account screening invitation (yes/no), period (before/after screening), region (other/Funen), and generations, along with interactions between periods and generations.

Figures captions

Figure 1: Published estimations of in situ and invasive breast cancer overdiagnosis (open symbols: two publications studying only invasive breast cancers quoted in the present text). Studies conducted on aggregated data give generally higher estimations of overdiagnosis than studies conducted on individual data. Source: Ripping et al. [1]. Updated by C. Hill

Figure 2: Overdiagnosis estimation, example of screening for neuroblastoma in Germany. Based on Schilling et al. and Spix et al. [2,3].

Control and test regions have a comparable population size, with 1.1 and 1.5 million children, respectively. Incidence is expressed in arbitrary units.

2a: Incidence is displayed as a function of age, and generalized neuroblastoma screening takes place at one year of age. There is logically no difference in incidence between control and test regions before screening age (<1-year-old). The screening program causes an increased incidence of cases immediately after screening at age 1, a decrease shortly afterwards, and a return to normal at around age 5.

2b: If there is no overdiagnosis, the number of cases additionally diagnosed during screening (solid green) should be equal to the sum of the number of missing cases, which would have been diagnosed later if there had been no screening (faded green).

2c: In the case of overdiagnosis, screening reveals an additional number of cases that would never have been clinically important enough to be diagnosed otherwise (red).

2d: The actual difference between the regions with and without screening was estimated to be 6.9/100,000, which translates to an overdiagnosis of 49%. According to this estimation, around half of neuroblastoma diagnosed during screening would have regressed spontaneously or would, at least, never have become clinical enough to be diagnosed, leading to unnecessary and potentially invasive treatment.

Figure 3: Lexis diagrams of the Funen overdiagnosis experiment, based on Njor et al. [4]. Generations can be followed on diagonals.

3a: Only women born between 01/11/1923 and 01/11/1943, who were 50 to 69 at the start of screening (01/11/1993), were invited to screening.

3b: In order to have sufficient follow-up time (follow-up ended on 31/12/2009), screened women born after 1933 were not included in the study. The screening area is shown in yellow and the follow-up area in grey. In the second and third rounds (1993-1999), women were invited again, even if they were over 70; hence, the extra upper trapezoid in the "screening" area.

3c: When following the screened population (S), several periods can be identified: first screenings (red), later screenings (orange), and 3 follow-up periods: 0-3 years (green), 4-7 years (light blue), and ≥ 8 years (dark blue) from the end of invitation to screening. The comparison between the screened (S) and the historical control population (H) is performed within each period.

Figure 4: Incidence of breast cancer as a function of age in Funen with screening (green), compared to a historical control group (Funen in a different period, red), to a

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3 *national control group (other regions, same period, **solid black line**), and to a*
4 *historical national control group (other regions, different period, **dashed black line**).*
5 *Adapted from Njor et al. 2018 [6].*
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9 **Figure 5:** *Incidence of breast cancer in Funen, compared to control. The incidence of*
10 *breast cancer observed in Funen during screening (in the same colours as in figure*
11 *3c) is compared in each period to the incidence in Funen estimated by the model in*
12 *the absence of screening (in grey).*
13
14

15
16 **Figure 6:** *Data analysed by Jørgensen (2009) to estimate overdiagnosis in Denmark*
17 *[8]. Under the aggregated data hypothesis, some women who were over 70 years of*
18 *age at the beginning of screening, and therefore have never been screened, are*
19 *included in the post-screening follow-up. These women are older and therefore at*
20 *greater risk of cancer; hence, this leads to an overestimation of risk. Similarly, some*
21 *women were not followed up so no hypothesis on their future incidence can be*
22 *explored.*
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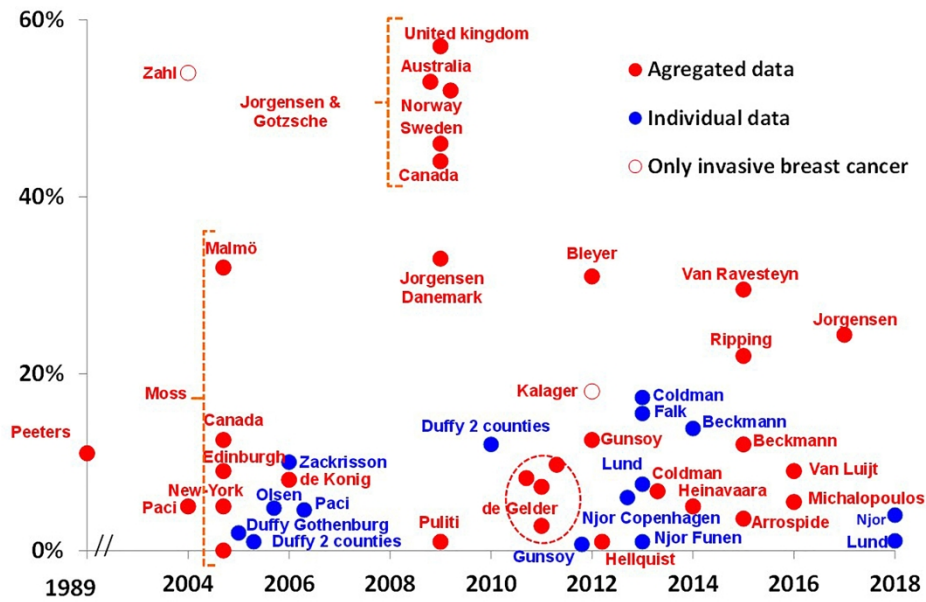


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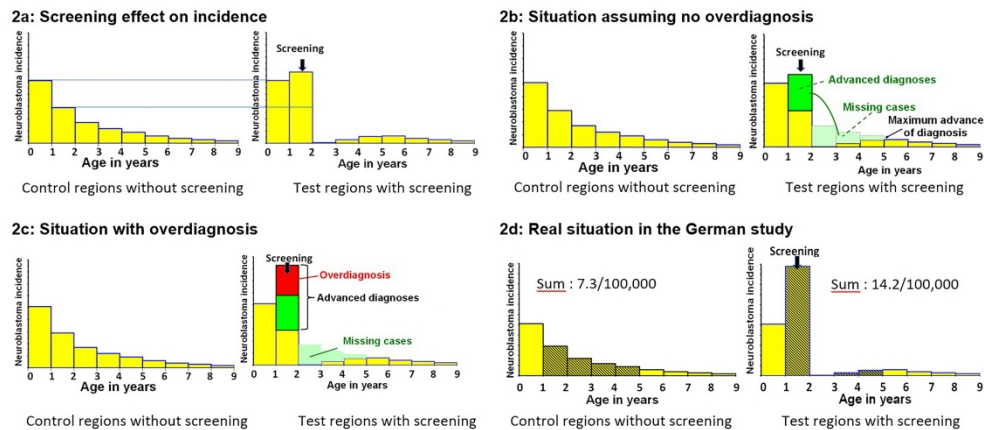


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2d: The actual difference between the regions with and without screening was estimated to be 6.9/100,000, which translates to an overdiagnosis of 49%. According to this estimation, around half of neuroblastoma diagnosed during screening would have regressed spontaneously or would, at least, never have become clinical enough to be diagnosed, leading to unnecessary and potentially invasive treatment.

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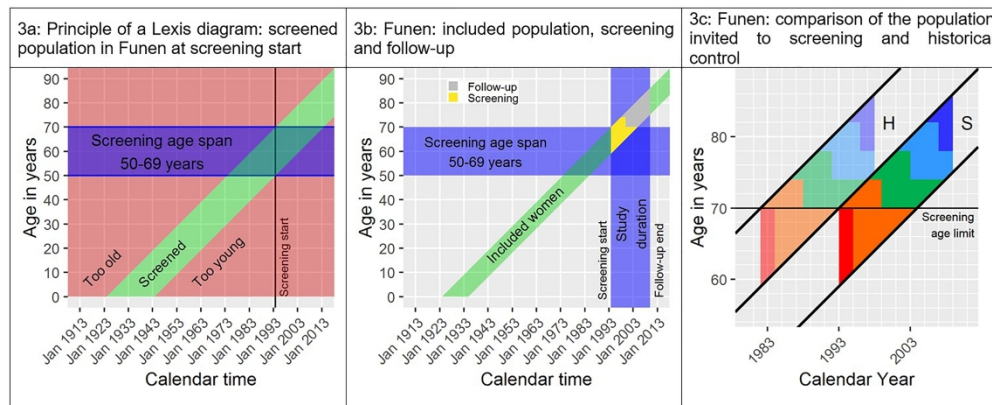


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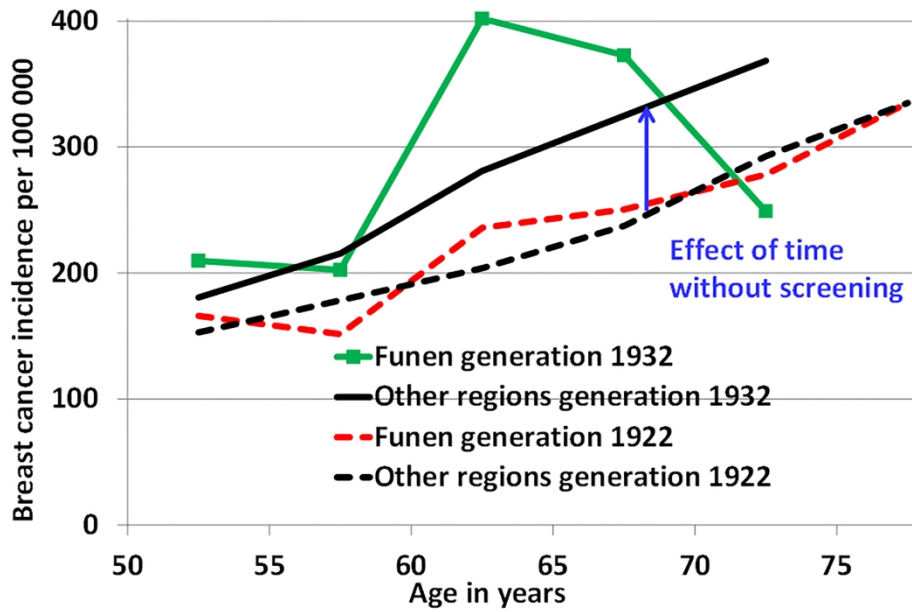


Figure 4: Incidence of breast cancer as a function of age in Funen with screening (green), compared to a historical control group (Funen in a different period, red), to a national control group (other regions, same period, solid black line), and to a historical national control group (other regions, different period, dashed black line). Adapted from Njor et al. 2018 [6].

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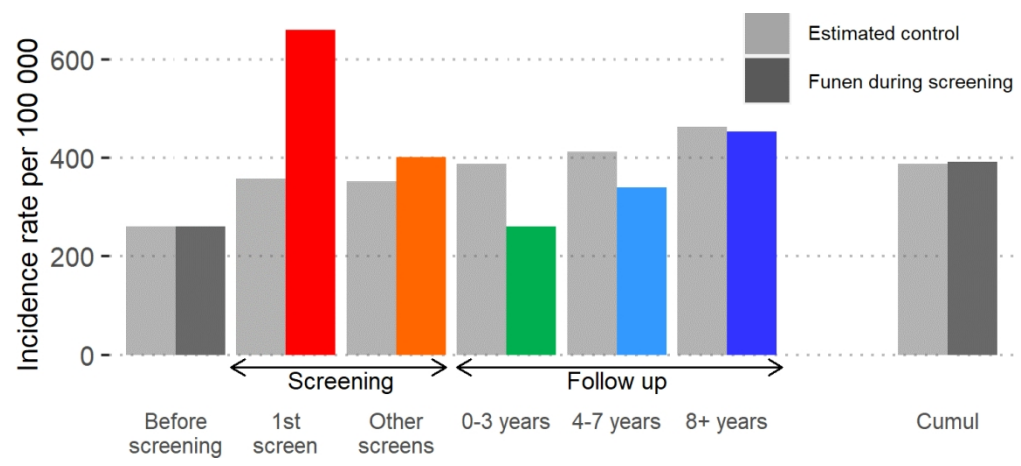


Figure 5: Incidence of breast cancer in Funen, compared to control. The incidence of breast cancer observed in Funen during screening (in the same colours as in figure 3c) is compared in each period to the incidence in Funen estimated by the model in the absence of screening (in grey).

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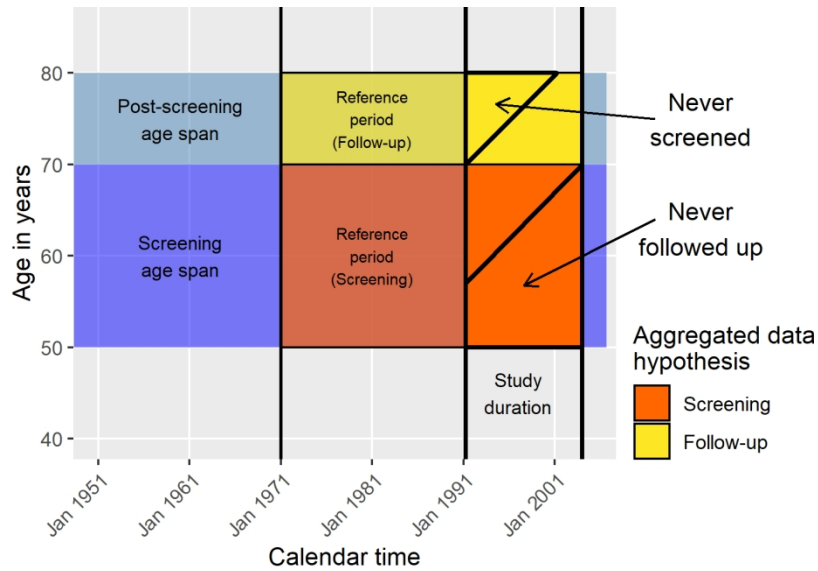


Figure 6: Data analysed by Jørgensen (2009) to estimate overdiagnosis in Denmark [8]. Under the aggregated data hypothesis, some women who were over 70 years of age at the beginning of screening, and therefore have never been screened, are included in the post-screening follow-up. These women are older and therefore at greater risk of cancer; hence, this leads to an overestimation of risk. Similarly, some women were not followed up so no hypothesis on their future incidence can be explored.

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The estimations of overdiagnosis in breast cancer screening vary between 0% and over 50%: why?

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The estimations of overdiagnosis in breast cancer screening vary between 0% and over 50%: why?

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Abstract

Background

Published estimations of the extent of breast cancer overdiagnosis vary widely, and there have been heated debates around these estimations. Some high estimates have even been the basis of campaigns against national breast cancer screening programs. Identifying some of the sources of heterogeneity between different estimates would help to clarify the issue.

Methods

The simple case of neuroblastoma - a childhood cancer - screening is used to describe the basic principle of overdiagnosis estimation. The more complicated mechanism of breast cancer overdiagnosis is described based on data from Denmark.

Findings

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3 Analysis of the data from Denmark demonstrates the importance of using individual
4 patients' data and identifies the use of aggregated data as the main reason for
5 overestimation of overdiagnosis.
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10 **Interpretation**

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12 Many estimates of overdiagnosis associated with breast cancer screening programs
13 are serious overestimations.
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1. Introduction

Many countries have a national breast cancer screening program in which all women belonging to a specific age-group are invited to have regular mammograms. These programs have been criticized, with claims that their benefit has been overestimated and that the risk of overdiagnosis has been understated. Here, overdiagnosis is defined as the diagnosis, by a screening procedure, of a cancer that would never have become symptomatic during the life of the person.

Both in situ and invasive cancers will be included in the estimation of overdiagnosis, since an overdiagnosed in situ breast cancer leads to an unnecessary treatment, which can include a mastectomy, a reconstructive surgery, and a cosmetic surgery on the other breast to restore symmetry.

The estimations of overdiagnosis in breast cancer screening vary between 0% and more than 50% (Figure 1), and the variety of these estimations contributes to the vigorous debate on the usefulness of breast cancer screening programs[1]. Since it is extremely unlikely that overdiagnosis varies to such a large extent from one program to another, one needs to study possible causes for this observed heterogeneity.

2. Estimation Methods

The ideal approach to estimate the overdiagnosis rate would be to use data from randomized controlled trials on breast cancer screening in which the participants in the control group were not offered screening at the end of the trial. Using data from trials does not come without bias if the post screening follow-up is not long enough. The methodology of estimation itself can also be controversial, as different confidence interval calculations could under or overestimate the uncertainty [2]. The only such trials are the two Canada trials and part of the Malmö trial and the performance of the Canada trials has been questioned[3]. Thus, we have to rely on

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3 observational studies, among which the best option is a cohort study with individual
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5 patient data.
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10 **3. Screening for neuroblastoma**

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12 We shall start by introducing some basic concepts about screening diagnosis, using
13
14 the example of the screening for neuroblastoma, a paediatric cancer of neuroblasts
15
16 (specialized nerve cells). The screening test is a measurement of urinary
17
18 catecholamines, which are hormones produced by neuroblastoma cells. A study
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20 conducted in Germany compared the incidence of neuroblastoma in regions without
21
22 screening and in experimental regions where screening of one-year-old children was
23
24 systematically offered [4].
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29 Such a screening program causes an increased incidence of cases immediately after
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31 screening (age 1 for neuroblastoma), a decrease shortly afterwards, and a return to
32
33 normal thereafter (around age 5 for neuroblastoma) (Figure 2a) [5]. In theory, the
34
35 screening program should allow the detection of the same number of cases, only
36
37 earlier (Figure 2b). Therefore, if there is no overdiagnosis, the number of cases
38
39 additionally diagnosed during screening (solid green) is equal to the number of cases
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41 that would have been diagnosed later, if there was no screening. Thus,
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43 overdiagnosis is measured by the difference between these two numbers (Figure 2c).
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45
46 In the German study, there were 7.3 and 14.2 cases per 100,000 children,
47
48 respectively, in the control and experimental regions (Figure 2d). Overdiagnosis is
49
50 the difference between these cumulative incidences, generally expressed as a
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52 percentage. Here, it represented 49% $[(14.2-7.3)/14.2]$ of the cases found in the
53
54 population invited to screening.
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3 This simple example shows the importance of the follow-up duration in correctly
4 estimating the amount of overdiagnosis. In the most extreme case, one would
5 compare the incidences observed at one year of age only, which would then attribute
6 overdiagnosis to all cases with a diagnosis brought forward by screening. Figure 2b
7 shows that the incidence of neuroblastoma at age 5 and over is again the same in
8 the two populations, which is why overdiagnosis has been estimated by comparing
9 the cumulative incidence with and without screening between 12 and 60 months of
10 age (Figure 2d, based on reference [4]).
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21 This study showed that screening for neuroblastoma at one year of age identified
22 many cases that would have regressed spontaneously. In the end, almost half of the
23 diagnoses were unnecessary and and detrimental to the child and his/her family;
24 therefore, this screening is no longer offered.
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30 **4. Breast cancer screening: example of the Funen data**

31 **The estimation of overdiagnosis**

32
33 To evaluate the amount of screening-induced overdiagnosis in breast cancer, we
34 shall use data from Denmark, as studied by Njor et al. [6]. The data used were
35 individual data, i.e., for each woman, her date of birth, history of mammography, and,
36 where applicable, dates of breast cancer diagnosis and death.
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44 This type of screening is a very different situation: in breast cancer screening
45 programs, the same woman may be invited several times, at different ages, whereas
46 children in the neuroblastoma study were all screened only once at 12 months old.
47 Thus, while age was sufficient to evaluate overdiagnosis in neuroblastoma, one
48 needs to take both age and calendar time into account to understand overdiagnosis
49 in breast cancer, which adds a layer of complexity. This breast cancer study
50 measured overdiagnosis by comparing the incidence of breast cancer in several
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3 places in Denmark (Funen Island, where there was a screening program, versus
4 other regions, where there was not) and during several periods (at the time of the
5 screening program versus beforehand).
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10 To describe the screening experience of a population over time, a Lexis diagram is
11 often used. An example is presented in Figure 3a: the horizontal axis represents the
12 calendar time, and the vertical axis represents the age of the person. Thus, the
13 trajectory of a given woman is a diagonal, starting at age 0 on her date of birth. A
14 generation can therefore be represented by a parallelogram. In Funen Island, the
15 screening program started on November 1, 1993, and the whole female population
16 aged 50 to 69 was invited.
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26 Each screening round lasted two years; therefore, the first round spanned from
27 November 1, 1993 to October 31, 1995. During the first three rounds, women were
28 invited again, even if they were over age 70. Figure 3b shows the study inclusion
29 design on a Lexis diagram. The study followed all patients from screening start until
30 31/12/2009 at the latest. Therefore, in order to have sufficient follow-up time, Njor et
31 al. included only patients aged 59 to 70 on November 1, 1993, as younger patients
32 would not have been followed for long enough [6]. In the figure, the intersection of the
33 “study duration” area, the “screening age span” area, and the “included women” area
34 identifies the screened population during screening (yellow) and during follow-up
35 (grey).
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49 Since Funen was not the experimental arm of a randomized trial, there was no
50 obvious control population allowing direct estimation of overdiagnosis. Thus, to
51 evaluate the extent of overdiagnosis, one needs to estimate the incidence expected
52 in Funen without screening.
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3 Two types of potential control populations can be considered: 1) the population of a
4 region without screening at the time when screening was offered in the experimental
5 region, allowing a comparison between “here with screening” and “elsewhere without
6 screening”, and 2) the population in the experimental region before screening,
7 allowing a comparison between “before without screening” and “after with screening”.
8
9 In the study of Funen, the control data available were data from Danish regions
10 without screening at the time of screening in Funen (generation November 1, 1923-
11 October 31, 1934), data from Funen before screening (generation November 1,
12 1912-October 31, 1923), and data from Danish regions without screening before the
13 introduction of screening in Funen (generation November 1, 1912-October 31, 1923).
14 Figure 3c is the Lexis diagram of the study period for women aged 60 and higher,
15 representing a comparison of the studied screened population (S, generation 1923-
16 1934) to the local historical control population (H, generation 1912-1923). Njor et al.
17 identified five periods of observation in the screened population: the first screening
18 round (prevalence screening), the later screening rounds (incidence screening),
19 which included women aged 70+ for the first three rounds, and three periods
20 corresponding to follow-up 0 to 3 years, 4 to 7 years, and 8+ years from the end of
21 invitation to screening, respectively [6]. By comparing each period of observation to
22 its historical situation, it is possible to estimate the number of cases that would have
23 been diagnosed in Funen if there was no screening program. However, this is still
24 only half of the solution, as it would not take into account the effect of geography.

51 **Simplified presentation of overdiagnosis estimation in Funen**

52 To understand the estimation of the breast cancer incidence that would be expected
53 if screening did not occur in Funen at the time of screening, let's focus on two one-
54 year generations: 1) women born in 1922 who were 71 on 1/11/1993 and, hence,
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3 were never invited to screening; and 2) women born in 1932 who were 61 on
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5 1/11/1993 and, hence, were invited to screening.
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8 Table 1 and the corresponding Figure 4 show the incidence as a function of age in
9
10 these two generations, in Funen versus in other regions. Before screening (1922
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12 generation), the incidence was rather similar in Funen (dashed red line) and in other
13
14 regions (dashed black line), the data being more erratic in Funen due to its
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16 population being eight times lower than in the other regions. In the other regions,
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18 where there was no screening, the breast cancer incidence increased at all ages
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20 between the 1922 generation (black dashed line) and the 1932 generation (black
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22 solid line). This can be explained by the improvement in imaging and diagnostic
23
24 techniques, among other things, during these 10 years.
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29 Therefore, a simple estimation of the incidence that would be expected in Funen if
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31 there was no screening in the 1932 generation can be obtained by applying this
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33 estimation of the effect of time to the incidence observed in Funen in the 1922
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35 generation. In practice, this is done by increasing the incidence observed in Funen in
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37 the 1922 generation, or a smoothed version of it, by the linear increase observed in
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39 the other regions. This is a partial view of the data from Denmark, which is shown
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41 here just to illustrate the principle of the method. Using the totals in Table 1 would
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43 lead to a ratio of cumulative incidences equal to $1.03 \left[\frac{1436 \times 1065}{1082 \times 1371} \right]$;
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45 hence, giving a 3% estimation of overdiagnosis.
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49 **Overdiagnosis estimation in Funen**

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51 The analysis by Njor et al. is actually more complete and relies on a mathematical
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53 model including screening invitation (yes/no), period (before/after screening), region
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55 (other/Funen), and generations, along with interactions between periods and
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57 generations [6].
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3 As described in Table 2 and the corresponding Figure 5, this model allows an
4 estimation of the incidence of breast cancer in Funen in the case where there was no
5 screening program, taking into account all the above-mentioned factors. It is then
6 possible to compare the incidence of breast cancer in both populations, separately in
7 each generation. By analogy, this is the equivalent of Figure 2d, for which it was
8 possible to place the age directly on the x-axis, as the screening was performed at
9 the same age for everyone.

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11 This leads to an estimation of overdiagnosis of 1%, based on the data observed in
12 Funen, addressing possible differences in the incidence between periods, between
13 Funen and the other regions, and between generations, as well as possible
14 interactions.

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16 In their article, Njor et al. also present a 5% estimation based on the data observed in
17 Copenhagen, where screening started on January 1, 1991, and concluded with a
18 global estimation of 4% overdiagnosis, based on all the data available in Denmark
19 [6].

20 **5. Analysis of aggregated data**

21
22 The data presented by Njor et al. are individual data, allowing the follow-up of each
23 woman, invited to screening or not, residing in Funen or in another region, including
24 the relevant dates (of birth, of screening invitation, of actual screening, of diagnosis,
25 and of death) [6].

26
27 However, a large number of overdiagnosis estimations rely on aggregated data.
28 These aggregated data are incidences observed by periods and by age-groups,
29 which are publicly available for breast cancer in many countries, hence the popularity
30 of their analysis.

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3 To understand the difference between aggregated and individual data, the Lexis
4 diagram is again useful. Jørgensen et al. estimated breast cancer overdiagnosis in
5 Denmark using aggregated data from two periods, 1971-1990 (without screening)
6 and 1991-2003 (with screening) in two age-groups: 50 to 69 and 70 to 79 [7].
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8 Therefore, these four populations are represented by four rectangles in the Lexis
9 diagram (Figure 6), instead of parallelograms corresponding to the follow-up of
10 generations.
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19 Jørgensen et al. first estimated the relative risk of breast cancer in the 50 to 69 age
20 group during the screening period (solid orange rectangle) as compared to the risk in
21 the same age group during the reference period (faded orange rectangle) [7]. They
22 used this relative risk to estimate the initial excess of cases, due to screening. They
23 then estimated the same relative risk in the 70-79 age group (solid and faded yellow
24 rectangles), and used it to estimate the post-screening deficit, the number of cases
25 that would have been diagnosed later if there was no screening. By subtracting the
26 post-screening deficit from the initial excess, they estimated the number of “falsely”
27 diagnosed breast cancers, which was translated to a 33% rate of overdiagnosis.
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40 Two major flaws with this design are shown on Figure 6. The first is that a fraction of
41 the patients, shown in the upper yellow triangle, were never screened, because they
42 were older than the upper age-limit for screening at the beginning of the screening
43 period. The inclusion of these unscreened older patients in the “post-screening”
44 follow-up overestimates the overdiagnosis rate. The second flaw is that the screened
45 patients in the lower orange trapezoid were never followed up, so there is no
46 information on a possible compensatory drop in later incidence. Moreover, this
47 design cannot adjust for the evolution of medical techniques and imaging over time.
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6. Discussion

Another paper by Njor et al. reviewed five of the most quoted studies, which had produced high estimates of overdiagnosis (some of these studies considered only invasive breast cancers) [8–13]. The data and the method used in each of these studies were identified, and each method was then applied to data from Denmark, adapting the timing to correspond to the timing of screening in Funen. Njor et al.'s 2018 study shows that using these methods leads to mistakenly high estimates of overdiagnosis, explained essentially by a too short duration of follow-up and by an inadequate estimation of the incidence expected without screening in the population invited to screening [8].

Follow-up duration

The first problem is a too short follow-up duration in the populations that are being compared. Similar to the neuroblastoma example, if one wants to compare the number of breast cancers in a screened and an unscreened population, the two populations must be followed-up long enough after the end of screening to avoid attributing the excess incidence observed by the screening to overdiagnosis.

Zahl et al., for instance, studied the incidence in a population invited to screening only during the first five years of the program (1996-2000), and could not measure the complete post-screening deficit [9]. They assumed it to be negligible based on the trend in breast cancer incidence in the population aged 70 or over. However, it is not the largely unscreened population aged 70 and over who should be considered: what is needed is the breast cancer incidence in the screened population at age 70 or over. Zahl et al. attributed the total excess incidence in the screened group to overdiagnosis, without taking into account the diagnoses brought forward by

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3 screening and therefore unobserved later. This explains the mistakenly high estimate
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5 of overdiagnosis.
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7 **The incidence expected in the absence of screening**

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10 In this case, where there are no data from randomized trials, one needs to estimate
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12 the breast cancer incidence that would be expected without screening in the
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14 population invited to screening. This is generally estimated on the basis of the
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16 observed incidence at the same time in an unscreened population geographically
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18 close to the population invited to screening, or in the population invited to screening
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20 before the start of the screening program. This requires some assumptions on the
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22 variation in breast cancer incidence with space and with time. The validity of the
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24 estimation depends on the validity of these assumptions.
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28 Jørgensen and Gotzsche estimated the expected incidence without screening by
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30 linearly extrapolating the pre-screening incidence and concluded that there was 30%
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32 to 40% overdiagnosis in Funen [11]. The same linear extrapolation performed in
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34 regions without screening would lead to an increase in the expected incidence
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36 between 12% and 17%. They have therefore attributed part of the increase, which
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38 was unrelated to screening but simply the effect of time, to overdiagnosis.
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42 Similarly, Zahl and Maehlen assumed the breast cancer incidence to have remained
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44 stable in Norway before and during screening, but the national registry data show
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46 that, in Norway just like in Denmark, breast cancer incidence was on the increase
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48 before screening started [12]. Taking this increasing trend into account reduces the
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50 estimation of overdiagnosis from 42% to 13%.
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53 **7. Conclusion**

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55 These analyses show empirically the diversity of estimations that can be obtained on
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57 the basis of the same data, using different methods. The estimations vary between
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3 0% and 55%, but some rely on data observed on the same women; hence, they
4 cannot all be correct.
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7 An important difference between studies is the use of individual versus aggregated
8 data. Figure 1 shows that all the studies providing estimates above 17% were based
9 on aggregated data; conversely, none of the studies based on individual data
10 provided estimates above 17%. However, some studies of aggregated data obtain
11 estimations below 17%; some of these use the simulation program MISCAN and
12 others were done by the Euroscreen working group.
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16 In conclusion, the estimation of overdiagnosis is a difficult exercise. The analysis of
17 individual data is generally less biased. The screened population must be followed-
18 up for several years after the end of screening, and the adequacy of the estimated
19 incidence expected without screening in the screened population must be discussed.
20
21 The exposure of the population to different breast cancer risk factors (age at first
22 pregnancy, number of children, alcohol consumption, and hormonal treatment for
23 menopause...) may have varied with time, and some of these factors have different
24 effects according to age. Some exposures may also vary with area. For instance, a
25 reduced use of hormonal treatment for menopause over time will lead to a reduction
26 in the incidence of post-menopausal breast cancer only, and the use of hormonal
27 treatment for menopause may have been reduced earlier in some parts of a country
28 than in others.
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32 In the end, any overdiagnosis estimation is an arithmetic combination of observed
33 data. The selection of the data and the way to combine them are more or less
34 judicious, depending on what the investigators have understood of the problem.
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Statements

Contributorship

Both DC and CH were involved in the conceptualisation of the overall paper and successive drafts, and contributed to the planning, conduct, and reporting of the work described in the article. CH was responsible of the design of the paper.

Competing interests

There are no competing interests for any author

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Tables

Table 1: Breast cancer incidence per 100,000 by age-group in Funen and in other regions for two generations, taken from Fig. 2 of Njor et al. 2018.

Age-group	Other regions, generation 1922	Other regions, generation 1932	Funen, generation 1922 (without	Funen, generation 1932 (with
			screening)	screening)
50-54	153	181	166	210
55-59	178	216	152	202
60-65	204	281	236	402
65-69	237	325	251	373
70-74	293	368	278	249
Total	1065	1371	1083	1436

Table 2: Breast cancer incidence per 100,000 observed in Funen for every generation, and model estimations in the case of no screening program. Adapted from Njor et al. 2013.

Period	Before screening	Invitation to screening		Follow-up post-screening			Cumulative over generations
		1st	Further	0-3 years	4-7 years	8+ years	
		screen	screens	after	after	after	
Observed	260	659	402	260	340	453	392
Expected*	260	358	352	388	411	462	387
RR	1.00	1.84	1.14	0.66	0.82	0.97	1.01

* The expected case number is calculated from model estimations, which take into account screening invitation (yes/no), period (before/after screening), region (other/Funen), and generations, along with interactions between periods and generations.

Figures captions

Figure 1: Published estimations of *in situ* and invasive breast cancer overdiagnosis (open symbols: two publications studying only invasive breast cancers quoted in the present text). Studies conducted on aggregated data give generally higher estimations of overdiagnosis than studies conducted on individual data. Source: Rippling et al. [1]. Updated by C. Hill. A comprehensive list of these studies is provided in Supplementary Data.

Figure 2: Overdiagnosis estimation, example of screening for neuroblastoma in Germany. Based on Schilling et al. and Spix et al. [4,5].

Control and test regions have a comparable population size, with 1.1 and 1.5 million children, respectively. Incidence is expressed in arbitrary units.

2a: Incidence is displayed as a function of age, and generalized neuroblastoma screening takes place at one year of age. There is logically no difference in incidence between control and test regions before screening age (<1-year-old). The screening program causes an increased incidence of cases immediately after screening at age 1, a decrease shortly afterwards, and a return to normal at around age 5.

2b: If there is no overdiagnosis, the number of cases additionally diagnosed during screening (solid green) should be equal to the sum of the number of missing cases, which would have been diagnosed later if there had been no screening (faded green).

2c: In the case of overdiagnosis, screening reveals an additional number of cases that would never have been clinically important enough to be diagnosed otherwise (red).

2d: The actual difference between the regions with and without screening was estimated to be 6.9/100,000, which translates to an overdiagnosis of 49%. According to this estimation, around half of neuroblastoma diagnosed during screening would have regressed spontaneously or would, at least, never have become clinical enough to be diagnosed, leading to unnecessary and potentially invasive treatment.

Figure 3: Lexis diagrams of the Funen overdiagnosis experiment, based on Njor et al. [6]. Generations can be followed on diagonals.

3a: Only women born between 01/11/1923 and 01/11/1943, who were 50 to 69 at the start of screening (01/11/1993), were invited to screening.

3b: In order to have sufficient follow-up time (follow-up ended on 31/12/2009), screened women born after 1933 were not included in the study. The screening area is shown in yellow and the follow-up area in grey. In the second and third rounds (1993-1999), women were invited again, even if they were over 70; hence, the extra upper trapezoid in the "screening" area.

3c: When following the screened population (S), several periods can be identified: first screenings (red), later screenings (orange), and 3 follow-up periods: 0-3 years (green), 4-7 years (light blue), and ≥ 8 years (dark blue) from the end of invitation to screening. The comparison between the screened (S) and the historical control population (H) is performed within each period.

Figure 4: Incidence of breast cancer as a function of age in Funen with screening (green), compared to a historical control group (Funen in a different period, red), to a

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3 *national control group (other regions, same period, **solid black line**), and to a*
4 *historical national control group (other regions, different period, **dashed black line**).*
5 *Each dot represents a five-year age group (e.g., a dot between 50 and 55 represents*
6 *the age group 50-54).*
7

8 *Adapted from Njor et al. 2018 [8].*
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10
11 **Figure 5:** *Incidence of breast cancer in Funen, compared to control. The incidence of*
12 *breast cancer observed in Funen during screening (in black) is compared in each*
13 *period to the incidence in Funen estimated by the model in the absence of screening*
14 *(in grey).*
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18 **Figure 6:** *Data analysed by Jørgensen (2009) to estimate overdiagnosis in Denmark*
19 *[10]. Under the aggregated data hypothesis, some women who were over 70 years of*
20 *age at the beginning of screening, and therefore have never been screened, are*
21 *included in the post-screening follow-up. These women are older and therefore at*
22 *greater risk of cancer; hence, this leads to an overestimation of risk. Similarly, some*
23 *women were not followed up so no hypothesis on their future incidence can be*
24 *explored.*
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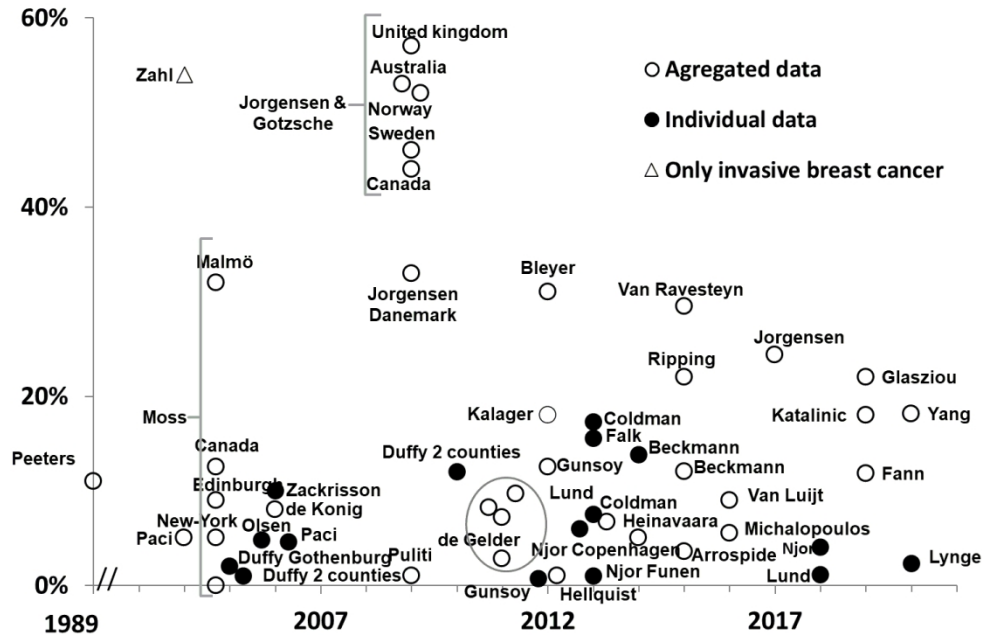


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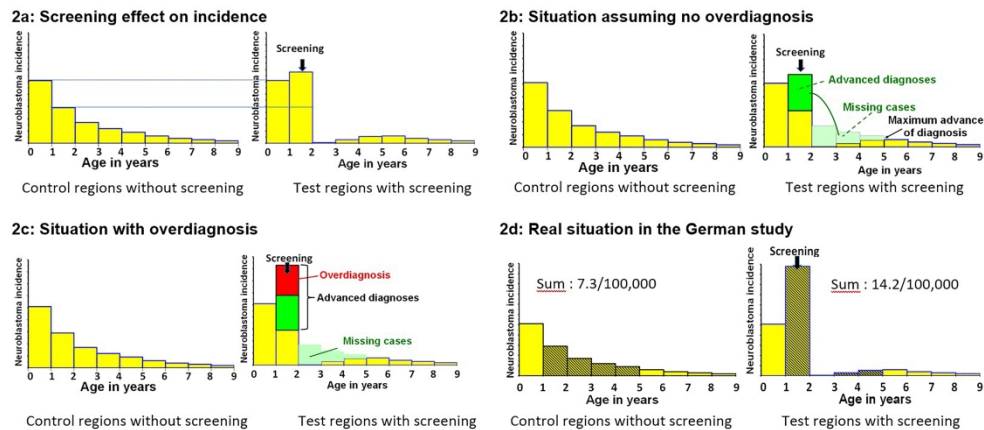


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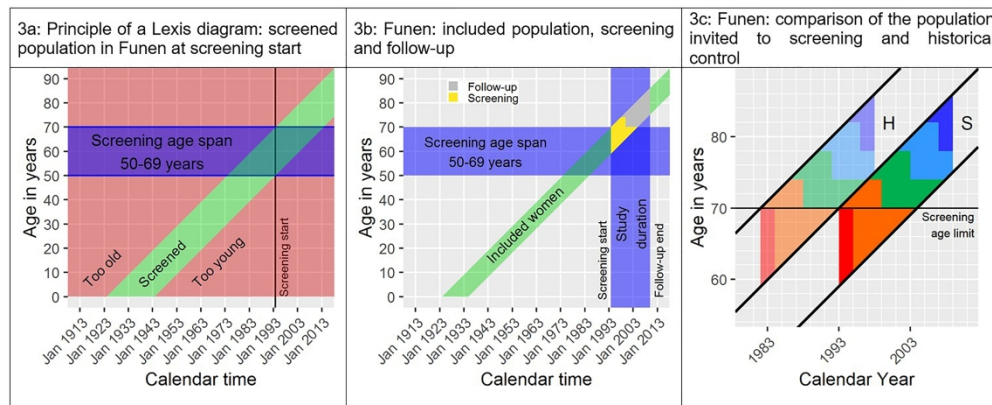


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3c: When following the screened population (S), several periods can be identified: first screenings (red), later screenings (orange), and 3 follow-up periods: 0-3 years (green), 4-7 years (light blue), and ≥ 8 years (dark blue) from the end of invitation to screening. The comparison between the screened (S) and the historical control population (H) is performed within each period.

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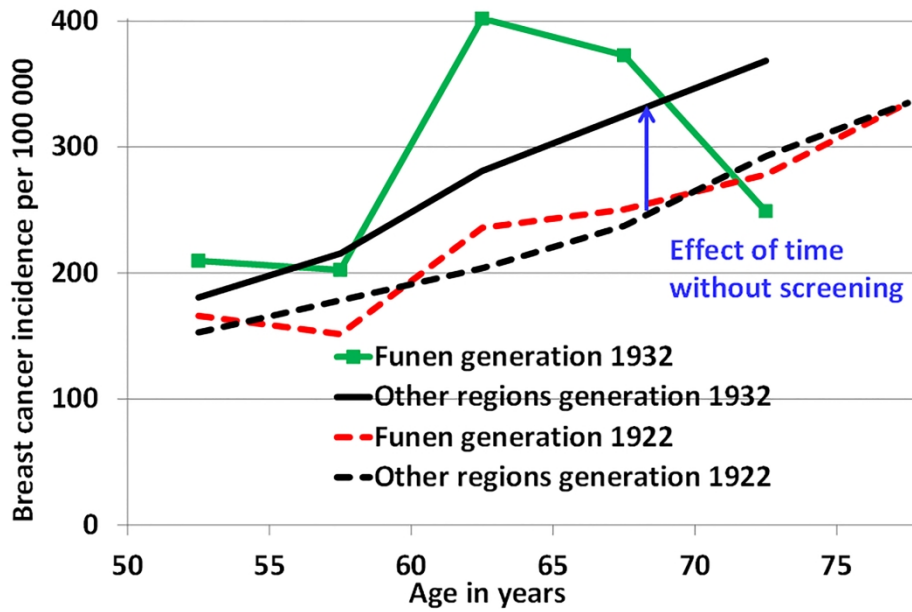


Figure 4: Incidence of breast cancer as a function of age in Funen with screening (green), compared to a historical control group (Funen in a different period, red), to a national control group (other regions, same period, solid black line), and to a historical national control group (other regions, different period, dashed black line). Adapted from Njor et al. 2018 [6].

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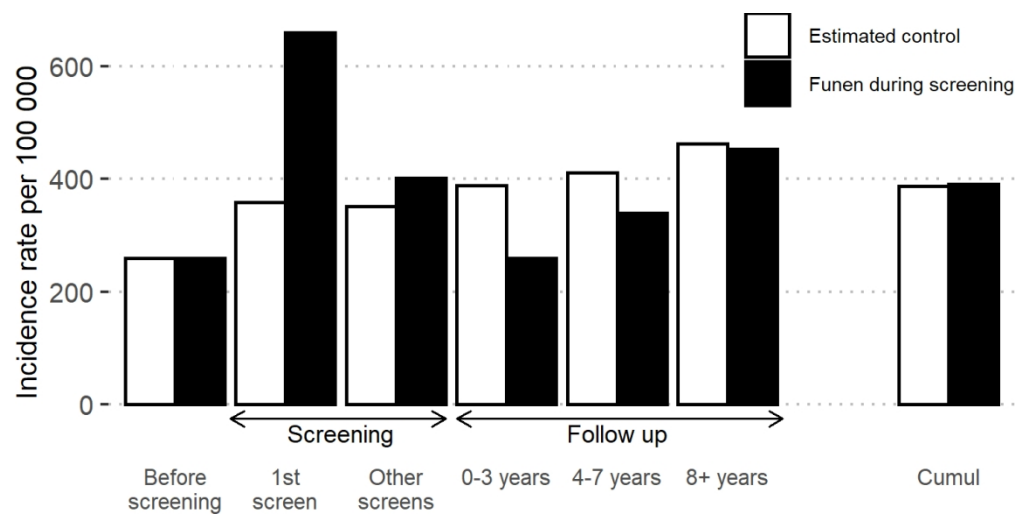


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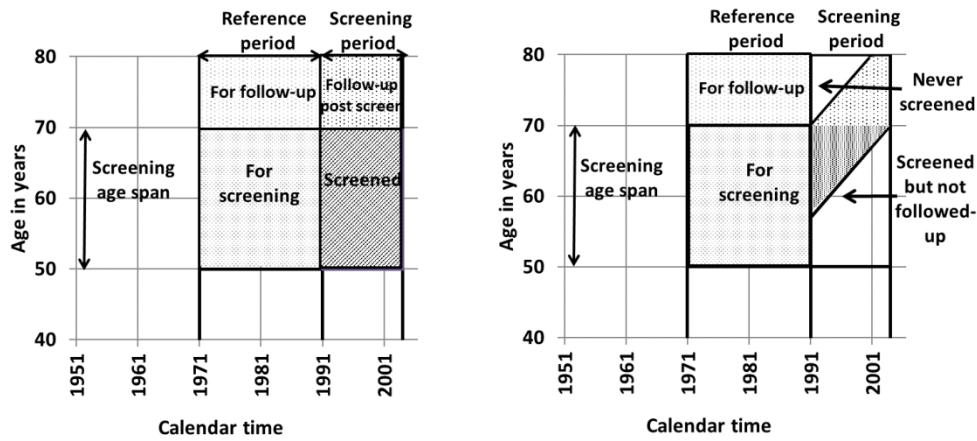


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Supplementary data

Comprehensive list of studies used to generate Figure 1:

1. Beckmann K, Duffy SW, Lynch J, Hiller J, Farshid G, Roder D. Estimates of over-diagnosis of breast cancer due to population-based mammography screening in South Australia after adjustment for lead time effects. *J Med Screen*. 2015;22(3):127–135.
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The estimations of overdiagnosis in breast cancer screening vary between 0% and over 50%: why?

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The estimations of overdiagnosis in breast cancer screening vary between 0% and over 50%: why?

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Abstract

Background

Published estimations of the extent of breast cancer overdiagnosis vary widely, and there have been heated debates around these estimations. Some high estimates have even been the basis of campaigns against national breast cancer screening programs. Identifying some of the sources of heterogeneity between different estimates would help to clarify the issue.

Methods

The simple case of neuroblastoma - a childhood cancer - screening is used to describe the basic principle of overdiagnosis estimation. The more complicated mechanism of breast cancer overdiagnosis is described based on data from Denmark, taking into account the type of data used, individual or aggregated.

Findings

The type of data used in overdiagnosis studies has a meaningful effect on the estimation: no study based on individual data provides an estimate higher than 17%,

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3 while studies based on aggregated data often provide estimates higher than 40%. This
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5 is too systematic to be random. The analysis of two Danish studies, one of each kind,
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7 highlights the biases that come with the use of aggregated data and shows how they
8
9 can lead to overdiagnosis.
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11 **Interpretation**

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14 Many estimates of overdiagnosis associated with breast cancer screening programs
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16 are serious overestimations.
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1. Introduction

Many countries have a national breast cancer screening program in which all women belonging to a specific age-group are invited to have regular mammograms. These programs have been criticized, with claims that their benefit has been overestimated and that the risk of overdiagnosis has been understated. Here, overdiagnosis is defined as the diagnosis, by a screening procedure, of a cancer that would never have become symptomatic during the life of the person.

Both in situ and invasive cancers will be included in the estimation of overdiagnosis, since an overdiagnosed in situ breast cancer leads to an unnecessary treatment, which can include a mastectomy, a reconstructive surgery, and a cosmetic surgery on the other breast to restore symmetry.

The estimations of overdiagnosis in breast cancer screening vary between 0% and more than 50% (Figure 1), and the variety of these estimations contributes to the vigorous debate on the usefulness of breast cancer screening programs[1]. Since it is extremely unlikely that overdiagnosis varies to such a large extent from one program to another, one needs to study possible causes for this observed heterogeneity.

2. Estimation Methods

The ideal approach to estimate the overdiagnosis rate would be to use data from randomized controlled trials on breast cancer screening in which the participants in the control group were not offered screening at the end of the trial. Using data from trials does not come without bias if the post screening follow-up is not long enough. The methodology of estimation itself can also be controversial, as different confidence interval calculations could under or overestimate the uncertainty [2]. The only such trials are the two Canada trials and part of the Malmö trial and the performance of the

Canada trials has been questioned [3]. Thus, we have to rely on observational studies, among which the best option is a cohort study with individual patient data.

3. Screening for neuroblastoma

We shall start by introducing some basic concepts about screening diagnosis, using the example of the screening for neuroblastoma, a paediatric cancer of neuroblasts (specialized nerve cells). The screening test is a measurement of urinary catecholamines, which are hormones produced by neuroblastoma cells. A study conducted in Germany compared the incidence of neuroblastoma in regions without screening and in experimental regions where screening of one-year-old children was systematically offered [4].

Such a screening program causes an increased incidence of cases immediately after screening (age 1 for neuroblastoma), a decrease shortly afterwards, and a return to normal thereafter (around age 5 for neuroblastoma) (Figure 2a) [5]. In theory, the screening program should allow the detection of the same number of cases, only earlier (Figure 2b). Therefore, if there is no overdiagnosis, the number of cases additionally diagnosed during screening (solid green) is equal to the number of cases that would have been diagnosed later, if there was no screening. Thus, overdiagnosis is measured by the difference between these two numbers (Figure 2c). In the German study, there were 7.3 and 14.2 cases per 100,000 children, respectively, in the control and experimental regions (Figure 2d). Overdiagnosis is the difference between these cumulative incidences, generally expressed as a percentage. Here, it represented 49% $[(14.2-7.3)/14.2]$ of the cases found in the population invited to screening.

This simple example shows the importance of the follow-up duration in correctly estimating the amount of overdiagnosis. In the most extreme case, one would compare

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3 the incidences observed at one year of age only, which would then attribute
4 overdiagnosis to all cases with a diagnosis brought forward by screening. Figure 2b
5 shows that the incidence of neuroblastoma at age 5 and over is again the same in the
6 two populations, which is why overdiagnosis has been estimated by comparing the
7 cumulative incidence with and without screening between 12 and 60 months of age
8 (Figure 2d, based on reference [4]).
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17 This study showed that screening for neuroblastoma at one year of age identified many
18 cases that would have regressed spontaneously. In the end, almost half of the
19 diagnoses were unnecessary and and detrimental to the child and his/her family;
20 therefore, this screening is no longer offered.
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25 26 **4. Breast cancer screening: example of the Funen data**

27 28 **The estimation of overdiagnosis**

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30 To evaluate the amount of screening-induced overdiagnosis in breast cancer, we shall
31 use data from Denmark, as studied by Njor et al. [6]. The data used were individual
32 data, i.e., for each woman, her date of birth, history of mammography, and, where
33 applicable, dates of breast cancer diagnosis and death.
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40 This type of screening is a very different situation: in breast cancer screening
41 programs, the same woman may be invited several times, at different ages, whereas
42 children in the neuroblastoma study were all screened only once at 12 months old.
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44 Thus, while age was sufficient to evaluate overdiagnosis in neuroblastoma, one needs
45 to take both age and calendar time into account to understand overdiagnosis in breast
46 cancer, which adds a layer of complexity. This breast cancer study measured
47 overdiagnosis by comparing the incidence of breast cancer in several places in
48 Denmark (Funen Island, where there was a screening program, versus other regions,
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3 where there was not) and during several periods (at the time of the screening program
4 versus beforehand).
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7 To describe the screening experience of a population over time, a Lexis diagram is
8 often used. An example is presented in Figure 3a: the horizontal axis represents the
9 calendar time, and the vertical axis represents the age of the person. Thus, the
10 trajectory of a given woman is a diagonal, starting at age 0 on her date of birth. A
11 generation can therefore be represented by a parallelogram. In Funen Island, the
12 screening program started on November 1, 1993, and the whole female population
13 aged 50 to 69 was invited.
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23 Each screening round lasted two years; therefore, the first round spanned from
24 November 1, 1993 to October 31, 1995. During the first three rounds, women were
25 invited again, even if they were over age 70. Figure 3b shows the study inclusion
26 design on a Lexis diagram. The study followed all patients from screening start until
27 31/12/2009 at the latest. Therefore, in order to have sufficient follow-up time, Njor et
28 al. included only patients aged 59 to 70 on November 1, 1993, as younger patients
29 would not have been followed for long enough [6]. In the figure, the intersection of the
30 “study duration” area, the “screening age span” area, and the “included women” area
31 identifies the screened population during screening (yellow) and during follow-up
32 (grey).
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46 Since Funen was not the experimental arm of a randomized trial, there was no obvious
47 control population allowing direct estimation of overdiagnosis. Thus, to evaluate the
48 extent of overdiagnosis, one needs to estimate the incidence expected in Funen
49 without screening.
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55 Two types of potential control populations can be considered: 1) the population of a
56 region without screening at the time when screening was offered in the experimental
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3 region, allowing a comparison between “here with screening” and “elsewhere without
4 screening”, and 2) the population in the experimental region before screening, allowing
5 a comparison between “before without screening” and “after with screening”.
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10 In the study of Funen, the control data available were data from Danish regions without
11 screening at the time of screening in Funen (generation November 1, 1923-October
12 31, 1934), data from Funen before screening (generation November 1, 1912-October
13 31, 1923), and data from Danish regions without screening before the introduction of
14 screening in Funen (generation November 1, 1912-October 31, 1923).
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21 Figure 3c is the Lexis diagram of the study period for women aged 60 and higher,
22 representing a comparison of the studied screened population (S, generation 1923-
23 1934) to the local historical control population (H, generation 1912-1923). Njor et al.
24 identified five periods of observation in the screened population: the first screening
25 round (prevalence screening), the later screening rounds (incidence screening), which
26 included women aged 70+ for the first three rounds, and three periods corresponding
27 to follow-up 0 to 3 years, 4 to 7 years, and 8+ years from the end of invitation to
28 screening, respectively [6]. By comparing each period of observation to its historical
29 situation, it is possible to estimate the number of cases that would have been
30 diagnosed in Funen if there was no screening program. However, this is still only half
31 of the solution, as it would not take into account the effect of geography.
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46 **Simplified presentation of overdiagnosis estimation in Funen**

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48 To understand the estimation of the breast cancer incidence that would be expected if
49 screening did not occur in Funen at the time of screening, let's focus on two one-year
50 generations: 1) women born in 1922 who were 71 on 1/11/1993 and, hence, were
51 never invited to screening; and 2) women born in 1932 who were 61 on 1/11/1993 and,
52 hence, were invited to screening.
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3 Figure 4 shows the incidence as a function of age in these two generations, in Funen
4 versus in other regions. Before screening (1922 generation), the incidence was rather
5 similar in Funen (dashed red line) and in other regions (dashed black line), the data
6 being more erratic in Funen due to its population being eight times lower than in the
7 other regions. In the other regions, where there was no screening, the breast cancer
8 incidence increased at all ages between the 1922 generation (black dashed line) and
9 the 1932 generation (black solid line). This can be explained by the improvement in
10 imaging and diagnostic techniques, among other things, during these 10 years.

11
12 Therefore, a simple estimation of the incidence that would be expected in Funen if
13 there was no screening in the 1932 generation can be obtained by applying this
14 estimation of the effect of time to the incidence observed in Funen in the 1922
15 generation. In practice, this is done by increasing the incidence observed in Funen in
16 the 1922 generation, or a smoothed version of it, by the linear increase observed in
17 the other regions. This is a partial view of the data from Denmark, which is shown here
18 just to illustrate the principle of the method.

19 **Overdiagnosis estimation in Funen**

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21 The analysis by Njor et al. is actually more complete and relies on a mathematical
22 model including screening invitation (yes/no), period (before/after screening), region
23 (other/Funen), and generations, along with interactions between periods and
24 generations [6].

25
26 As described in Table 1 and the corresponding Figure 5, this model allows an
27 estimation of the incidence of breast cancer in Funen in the case where there was no
28 screening program, taking into account all the above-mentioned factors. It is then
29 possible to compare the incidence of breast cancer in both populations, separately in
30 each generation. By analogy, this is the equivalent of Figure 2d, for which it was
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3 possible to place the age directly on the x-axis, as the screening was performed at the
4 same age for everyone.
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7 This leads to an estimation of overdiagnosis of 1%, based on the data observed in
8 Funen, addressing possible differences in the incidence between periods, between
9 Funen and the other regions, and between generations, as well as possible
10 interactions.
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14 In their article, Njor et al. also present a 5% estimation based on the data observed in
15 Copenhagen, where screening started on January 1, 1991, and concluded with a
16 global estimation of 4% overdiagnosis, based on all the data available in Denmark [6].
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23 **5. Analysis of aggregated data**

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25 The data presented by Njor et al. are individual data, allowing the follow-up of each
26 woman, invited to screening or not, residing in Funen or in another region, including
27 the relevant dates (of birth, of screening invitation, of actual screening, of diagnosis,
28 and of death) [6].
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35 However, a large number of overdiagnosis estimations rely on aggregated data. These
36 aggregated data are incidences observed by periods and by age-groups, which are
37 publicly available for breast cancer in many countries, hence the popularity of their
38 analysis.
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45 To understand the difference between aggregated and individual data, the Lexis
46 diagram is again useful. Jørgensen et al. estimated breast cancer overdiagnosis in
47 Denmark using aggregated data from two periods, 1971-1990 (without screening) and
48 1991-2003 (with screening) in two age-groups: 50 to 69 and 70 to 79 [7]. Therefore,
49 these four populations are represented by four rectangles in the Lexis diagram (Figure
50 6), instead of parallelograms corresponding to the follow-up of generations.
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3 Jørgensen et al. first estimated the relative risk of breast cancer in the 50 to 69 age
4 group during the screening period (solid orange rectangle) as compared to the risk in
5 the same age group during the reference period (faded orange rectangle) [7]. They
6 used this relative risk to estimate the initial excess of cases, due to screening. They
7 then estimated the same relative risk in the 70-79 age group (solid and faded yellow
8 rectangles), and used it to estimate the post-screening deficit, the number of cases
9 that would have been diagnosed later if there was no screening. By subtracting the
10 post-screening deficit from the initial excess, they estimated the number of “falsely”
11 diagnosed breast cancers, which was translated to a 33% rate of overdiagnosis.

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24 Two major flaws with this design are shown on Figure 6. The first is that a fraction of
25 the patients, shown in the upper yellow triangle, were never screened, because they
26 were older than the upper age-limit for screening at the beginning of the screening
27 period. The inclusion of these unscreened older patients in the “post-screening” follow-
28 up overestimates the overdiagnosis rate. The second flaw is that the screened patients
29 in the lower orange trapezoid were never followed up, so there is no information on a
30 possible compensatory drop in later incidence. Moreover, this design cannot adjust for
31 the evolution of medical techniques and imaging over time.

32 33 34 35 36 37 38 39 40 41 42 43 44 45 **6. Discussion**

46
47 Another paper by Njor et al. reviewed five of the most quoted studies, which had
48 produced high estimates of overdiagnosis (some of these studies considered only
49 invasive breast cancers) [8–13]. The data and the method used in each of these
50 studies were identified, and each method was then applied to data from Denmark,
51 adapting the timing to correspond to the timing of screening in Funen. Njor et al.’s 2018
52 study shows that using these methods leads to mistakenly high estimates of
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3 overdiagnosis, explained essentially by a too short duration of follow-up and by an
4 inadequate estimation of the incidence expected without screening in the population
5 invited to screening [8].
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9 **Follow-up duration**

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12 The first problem is a too short follow-up duration in the populations that are being
13 compared. Similar to the neuroblastoma example, if one wants to compare the number
14 of breast cancers in a screened and an unscreened population, the two populations
15 must be followed-up long enough after the end of screening to avoid attributing the
16 excess incidence observed by the screening to overdiagnosis.
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22 Zahl et al., for instance, studied the incidence in a population invited to screening only
23 during the first five years of the program (1996-2000), and could not measure the
24 complete post-screening deficit [9]. They assumed it to be negligible based on the trend
25 in breast cancer incidence in the population aged 70 or over. However, it is not the
26 largely unscreened population aged 70 and over who should be considered: what is
27 needed is the breast cancer incidence in the screened population at age 70 or over.
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The incidence expected in the absence of screening

In this case, where there are no data from randomized trials, one needs to estimate
the breast cancer incidence that would be expected without screening in the population
invited to screening. This is generally estimated on the basis of the observed incidence
at the same time in an unscreened population geographically close to the population
invited to screening, or in the population invited to screening before the start of the
screening program. This requires some assumptions on the variation in breast cancer

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3 incidence with space and with time. The validity of the estimation depends on the
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5 validity of these assumptions.
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8 Jørgensen and Gotzsche estimated the expected incidence without screening by
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10 linearly extrapolating the pre-screening incidence and concluded that there was 30%
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12 to 40% overdiagnosis in Funen [11]. The same linear extrapolation performed in
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14 regions without screening would lead to an increase in the expected incidence between
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16 12% and 17%. They have therefore attributed part of the increase, which was unrelated
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18 to screening but simply the effect of time, to overdiagnosis.
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21 Similarly, Zahl and Maehlen assumed the breast cancer incidence to have remained
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23 stable in Norway before and during screening, but the national registry data show that,
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25 in Norway just like in Denmark, breast cancer incidence was on the increase before
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27 screening started [12]. Taking this increasing trend into account reduces the estimation
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29 of overdiagnosis from 42% to 13%.
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32 33 **7. Conclusion**

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35 These analyses show empirically the diversity of estimations that can be obtained on
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37 the basis of the same data, using different methods. The estimations vary between 0%
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39 and 55%, but some rely on data observed on the same women; hence, they cannot all
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41 be correct.
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44 An important difference between studies is the use of individual versus aggregated
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46 data. Figure 1 shows that all the studies providing estimates above 17% were based
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48 on aggregated data; conversely, none of the studies based on individual data provided
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50 estimates above 17%. However, some studies of aggregated data obtain estimations
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52 below 17%; some of these use the simulation program MISCAN and others were done
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54 by the Euroscreen working group.
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3 In conclusion, the estimation of overdiagnosis is a difficult exercise. The analysis of
4 individual data is generally less biased. The screened population must be followed-up
5 for several years after the end of screening, and the adequacy of the estimated
6 incidence expected without screening in the screened population must be discussed.
7
8 The exposure of the population to different breast cancer risk factors (age at first
9 pregnancy, number of children, alcohol consumption, and hormonal treatment for
10 menopause...) may have varied with time, and some of these factors have different
11 effects according to age. Some exposures may also vary with area. For instance, a
12 reduced use of hormonal treatment for menopause over time will lead to a reduction in
13 the incidence of post-menopausal breast cancer only, and the use of hormonal
14 treatment for menopause may have been reduced earlier in some parts of a country
15 than in others.

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17 In the end, any overdiagnosis estimation is an arithmetic combination of observed data.
18 The selection of the data and the way to combine them are more or less judicious,
19 depending on what the investigators have understood of the problem.
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Statements

Contributorship

30 Both DC and CH were involved in the conceptualisation of the overall paper and
31 successive drafts, and contributed to the planning, conduct, and reporting of the work
32 described in the article. CH was responsible of the design of the paper.
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Competing interests

40 There are no competing interests for any author
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Tables

Table 1: Breast cancer incidence per 100,000 observed in Funen for every generation, and model estimations in the case of no screening program. Adapted from Njor et al. 2013.

Period	Before screening	Invitation to screening		Follow-up post-screening			Cumulative over generations
		1st screen	Further screens	0-3 years after	4-7 years after	8+ years after	
Observed	260	659	402	260	340	453	392
Expected*	260	358	352	388	411	462	387
RR	1·00	1·84	1·14	0·66	0·82	0·97	1·01

* The expected case number is calculated from model estimations, which take into account screening invitation (yes/no), period (before/after screening), region (other/Funen), and generations, along with interactions between periods and generations.

Figures captions

Figure 1: Published estimations of *in situ* and invasive breast cancer overdiagnosis (open symbols: two publications studying only invasive breast cancers quoted in the present text). Studies conducted on aggregated data give generally higher estimations of overdiagnosis than studies conducted on individual data. Source: Rippling et al. [1]. Updated by C. Hill. A comprehensive list of these studies is provided in Supplementary Data.

Figure 2: Overdiagnosis estimation, example of screening for neuroblastoma in Germany. Based on Schilling et al. and Spix et al. [4,5].

Control and test regions have a comparable population size, with 1.1 and 1.5 million children, respectively. Incidence is expressed in arbitrary units.

2a: Incidence is displayed as a function of age, and generalized neuroblastoma screening takes place at one year of age. There is logically no difference in incidence between control and test regions before screening age (<1-year-old). The screening program causes an increased incidence of cases immediately after screening at age 1, a decrease shortly afterwards, and a return to normal at around age 5.

2b: If there is no overdiagnosis, the number of cases additionally diagnosed during screening (solid green) should be equal to the sum of the number of missing cases, which would have been diagnosed later if there had been no screening (faded green).

2c: In the case of overdiagnosis, screening reveals an additional number of cases that would never have been clinically important enough to be diagnosed otherwise (red).

2d: The actual difference between the regions with and without screening was estimated to be 6.9/100,000, which translates to an overdiagnosis of 49%. According to this estimation, around half of neuroblastoma diagnosed during screening would have regressed spontaneously or would, at least, never have become clinical enough to be diagnosed, leading to unnecessary and potentially invasive treatment.

Figure 3: Lexis diagrams of the Funen overdiagnosis experiment, based on Njor et al. [6]. Generations can be followed on diagonals.

3a: Only women born between 01/11/1923 and 01/11/1943, who were 50 to 69 at the start of screening (01/11/1993), were invited to screening.

3b: In order to have sufficient follow-up time (follow-up ended on 31/12/2009), screened women born after 1933 were not included in the study. The screening area is shown in yellow and the follow-up area in grey. In the second and third rounds (1993-1999), women were invited again, even if they were over 70; hence, the extra upper trapezoid in the "screening" area.

3c: When following the screened population (S), several periods can be identified: first screenings (red), later screenings (orange), and 3 follow-up periods: 0-3 years (green), 4-7 years (light blue), and ≥ 8 years (dark blue) from the end of invitation to screening. The comparison between the screened (S) and the historical control population (H) is performed within each period.

Figure 4: Incidence of breast cancer as a function of age in Funen with screening (green), compared to a historical control group (Funen in a different period, red), to a national control group (other regions, same period, solid black line), and to a historical national control group (other regions, different period, dashed black line). Each dot

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3 represents a five-year age group (e.g., a dot between 50 and 55 represents the age
4 group 50-54).
5 Adapted from Njor et al. 2018 [8].
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9 **Figure 5:** Incidence of breast cancer in Funen, compared to control. The incidence of
10 breast cancer observed in Funen during screening (in black) is compared in each
11 period to the incidence in Funen estimated by the model in the absence of screening
12 (in grey).
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16 **Figure 6:** Data analysed by Jørgensen (2009) to estimate overdiagnosis in Denmark
17 [10]. Under the aggregated data hypothesis, some women who were over 70 years of
18 age at the beginning of screening, and therefore have never been screened, are
19 included in the post-screening follow-up. These women are older and therefore at
20 greater risk of cancer; hence, this leads to an overestimation of risk. Similarly, some
21 women were not followed up so no hypothesis on their future incidence can be
22 explored.
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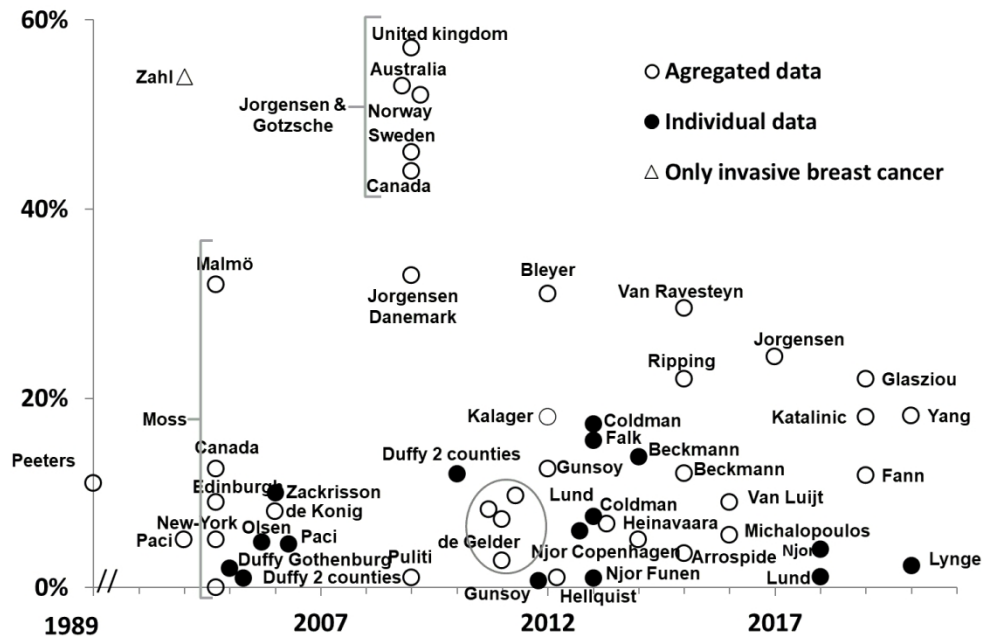


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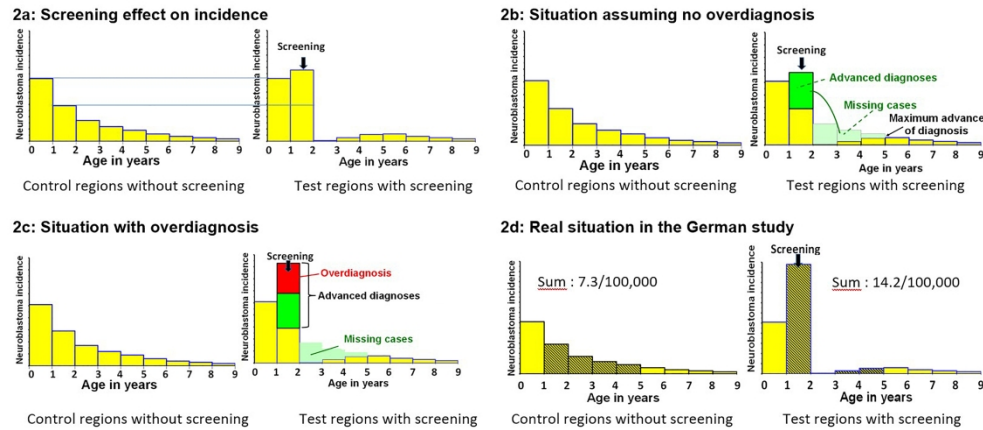


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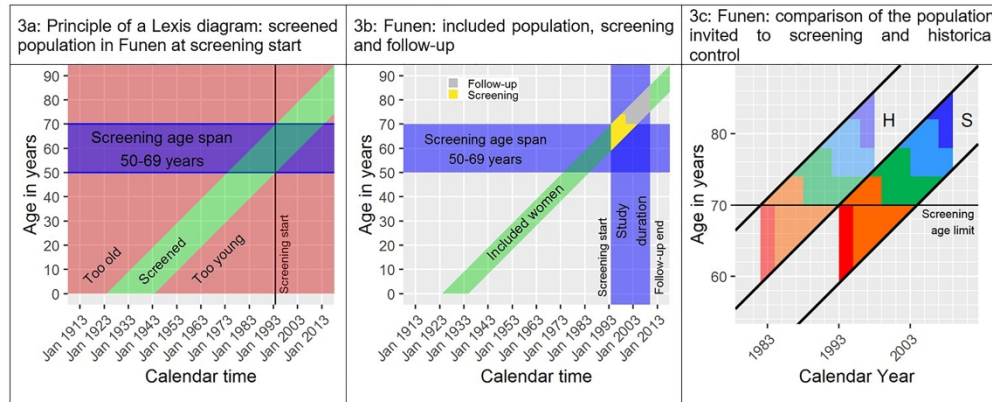


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3c: When following the screened population (S), several periods can be identified: first screenings (red), later screenings (orange), and 3 follow-up periods: 0-3 years (green), 4-7 years (light blue), and ≥ 8 years (dark blue) from the end of invitation to screening. The comparison between the screened (S) and the historical control population (H) is performed within each period.

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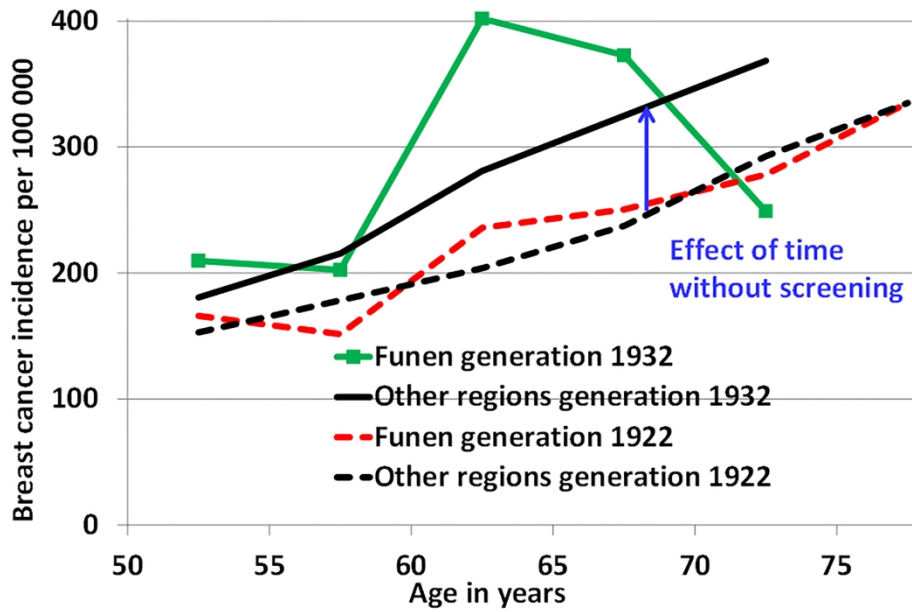


Figure 4: Incidence of breast cancer as a function of age in Funen with screening (green), compared to a historical control group (Funen in a different period, red), to a national control group (other regions, same period, solid black line), and to a historical national control group (other regions, different period, dashed black line). Adapted from Njor et al. 2018 [6].

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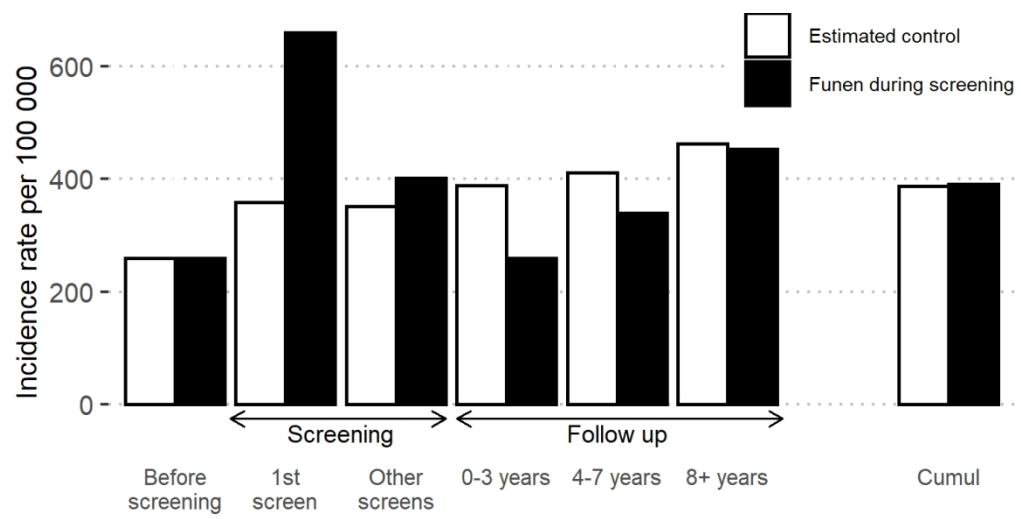


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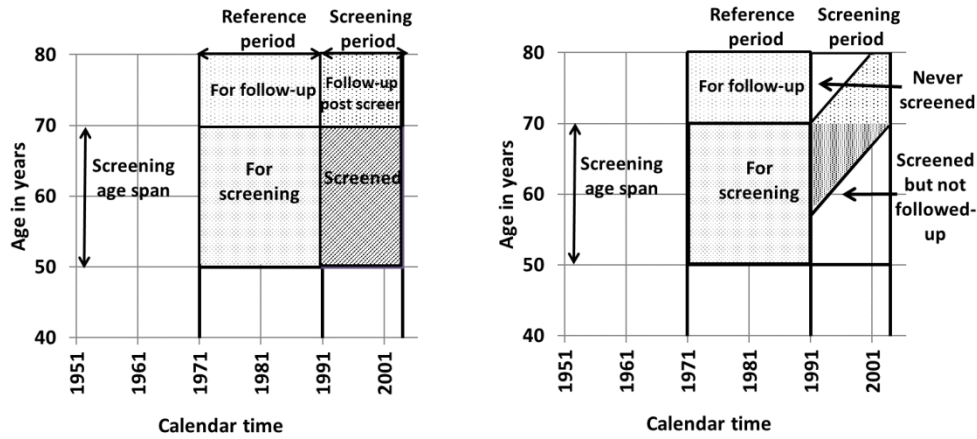


Figure 6: Data analysed by Jørgensen (2009) to estimate overdiagnosis in Denmark [9]. Under the aggregated data hypothesis, some women who were over 70 years of age at the beginning of screening, and therefore have never been screened, are included in the post-screening follow-up. These women are older and therefore at greater risk of cancer; hence, this leads to an overestimation of risk. Similarly, some women were not followed up so no hypothesis on their future incidence can be explored.

Supplementary data

Comprehensive list of studies used to generate Figure 1:

1. Beckmann K, Duffy SW, Lynch J, Hiller J, Farshid G, Roder D. Estimates of over-diagnosis of breast cancer due to population-based mammography screening in South Australia after adjustment for lead time effects. *J Med Screen*. 2015;22(3):127–135.
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