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Breast Cancer Screening in Denmark

A Cohort Study of Tumor Size and Overdiagnosis

Karsten Juhl Jørgensen, MD, DrMedSci; Peter C. Gøtzsche, MD, MSc; Mette Kalager, MD, PhD*; and Per-Henrik Zahl, MD, DrMedSci*

Background: Effective breast cancer screening should detect early-stage cancer and prevent advanced disease.

Objective: To assess the association between screening and the size of detected tumors and to estimate overdiagnosis (detection of tumors that would not become clinically relevant).

Design: Cohort study.

Setting: Denmark from 1980 to 2010.

Participants: Women aged 35 to 84 years.

Intervention: Screening programs offering biennial mammography for women aged 50 to 69 years beginning in different regions at different times.

Measurements: Trends in the incidence of advanced (>20 mm) and nonadvanced (≤20 mm) breast cancer tumors in screened and nonscreened women were measured. Two approaches were used to estimate the amount of overdiagnosis: comparing the incidence of advance and nonadvanced tumors among women aged 50 to 84 years in screening and nonscreening areas; and comparing the incidence for nonadvanced tumors among women aged 35 to 49, 50 to 69, and 70 to 84 years in screening and nonscreening areas.

Results: Screening was not associated with lower incidence of advanced tumors. The incidence of nonadvanced tumors increased in the screening versus prescreening periods (incidence rate ratio, 1.49 [95% CI, 1.43 to 1.54]). The first estimation approach found that 271 invasive breast cancer tumors and 179 ductal carcinoma in situ (DCIS) lesions were overdiagnosed in 2010 (overdiagnosis rate of 24.4% [including DCIS] and 14.7% [excluding DCIS]). The second approach, which accounted for regional differences in women younger than the screening age, found that 711 invasive tumors and 180 cases of DCIS were overdiagnosed in 2010 (overdiagnosis rate of 48.3% [including DCIS] and 38.6% [excluding DCIS]).

Limitation: Regional differences complicate interpretation.

Conclusion: Breast cancer screening was not associated with a reduction in the incidence of advanced cancer. It is likely that 1 in every 3 invasive tumors and cases of DCIS diagnosed in women offered screening represent overdiagnosis (incidence increase of 48.3%).

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For author affiliations, see end of text.

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* Drs. Kalager and Zahl contributed equally to this work.

Effective breast cancer screening should reduce the incidence of advanced tumors (1). Tumors larger than 20 mm at detection are usually considered advanced because they are equivalent to T2 or greater in the TNM (tumor, node, metastasis) classification system (2–4). Screening mammography detects many small tumors that would not have become clinically evident in the remaining lifetime without screening (overdiagnosis) (5). Whether screening reduces the incidence of advanced tumors has important therapeutic implications. Overdiagnosed lesions may be unnecessarily treated with surgery, chemotherapy, and radiation, which subjects women to the harms of therapy without benefit (6). Our study objectives were to examine the association of screening with a reduction in the incidence of advanced cancer and estimate the level of overdiagnosis in the Danish breast screening program.

Denmark provides a unique opportunity to estimate overdiagnosis because only 20% of the population aged 50 to 69 years was invited to participate in a mammography screening program for 17 years, which, to our knowledge, is the longest available period with differential mammography access in any country. Unlike studies in other settings that did not have a contemporaneous nonscreened group or nonscreened age groups (3, 4, 7, 8), we examine the association of screening with incidence of advanced cancer and estimate overdiagnosis using the contemporaneous same-age nonscreened group and nonscreened age groups as controls.

METHODS

Design

We conducted a cohort study using individual, anonymized data on tumor size for all Danish women aged 35 to 85 years diagnosed with invasive breast cancer during 1980 to 2010 from the Danish Breast Cancer Group (DBCG) and the Danish Cancer Registry (DCR). These independent databases cover all of Denmark and have been validated; about 1.2% of cases of breast cancer were missing or misdiagnosed (9). Tumors were verified histopathologically (9) and consid-

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Figure 1. Three-year moving averages of advanced breast tumors (>20 mm) in women aged 35 to 49 y (*A*), 50 to 69 y (*B*), and 70 to 84 y (*C*).

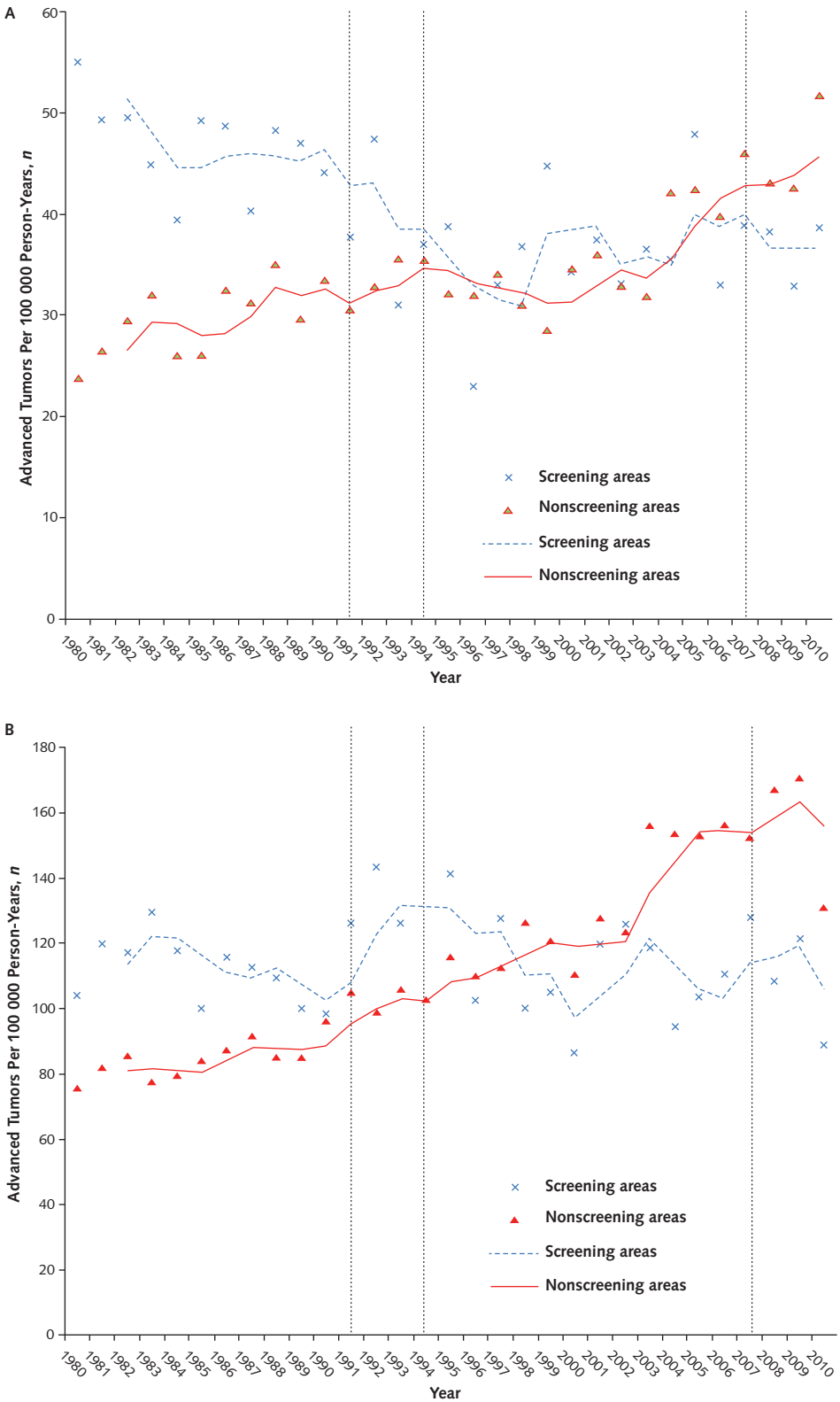

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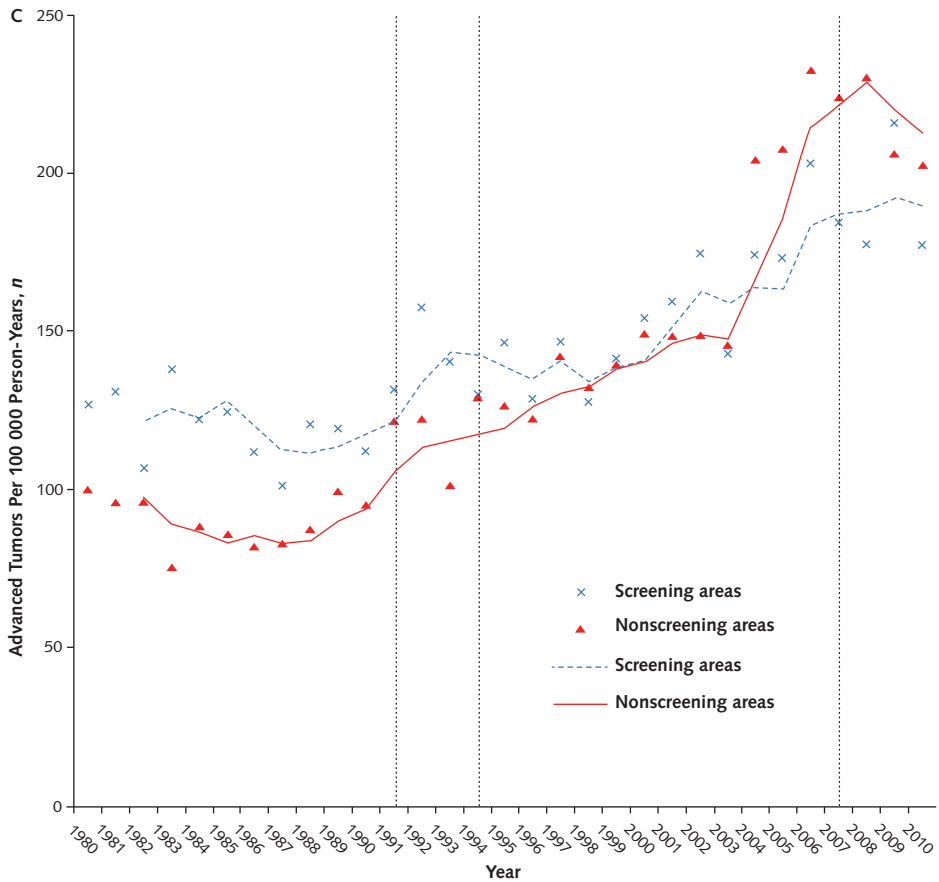
Figure 1–Continued



The vertical dotted lines indicate the year of introduction of breast screening in Copenhagen (1991), Funen (1994), and the remaining regions in Denmark (2007). (See **Supplement Figure 4**, available at www.annals.org, for separate incidence rates for Copenhagen and Funen.)

ered nonadvanced if they were 20 mm or less and advanced if greater than 20 mm in diameter (T2 to T4 in the TNM system) (2). Because the DCR did not record tumor size until 2004, we used DBCG data from 1980 to 2004. When we compared the DBCG database with the DCR after 2004, tumor size was not registered in 8% to 10% of the tumors in the DBCG database. We therefore used the DCR data after 2004. However, the DCR was missing the tumor size for 4% to 5% of tumors; thus, we excluded these tumors from our analyses. Registration of ductal carcinoma in situ (DCIS) was not mandatory in the DCR and DBCG before 2008 and 1989, respectively. Therefore, DCIS data were from the DBCG database for the entire observation period and are presented for the screened age group only because DCIS is mainly detected through screening. Statistics Denmark was the source of population size (10).

Breast Cancer Screening in Denmark

Organized breast cancer screening programs began in different regions at different times (Copenhagen in April 1991, Funen in 1993, and Frederiksberg in July 1994) and covered approximately 20% of the population (11). From late 2007, the remaining regions gradually introduced screening, but coverage was still incomplete in 2014 (12). Women aged 50 to 69 years were invited by mail to screening at a specified date and time. Screening was offered biennially and included 2-view mammography in the first round and 1-view mammography at subsequent rounds, except for women with dense breasts who always received 2-view mammography. The program did not include clinical breast examination. Screening results were mailed to women and their general practitioners within 10 working days. Women with abnormal results were referred to specialized units for additional testing. Participation rates in subsequent screening rounds were 62% in Copenhagen and 82% in Funen (11, 13). Danish women generally do not seek screening mammograms outside the organized program (14).

Statistical Analysis

We used a before–after approach to define screening and nonscreening areas. The screening areas were Copenhagen, Frederiksberg, and Funen, and the remaining 80% of Denmark was the nonscreening area. We merged Frederiksberg and Copenhagen because Frederiksberg is geographically surrounded by Copenhagen (43 000 women in the first round collectively). For Copenhagen and Frederiksberg, the prescreening

Table 1. Annual Percentage of Change in Incidence (95% CI) in the Screening and Nonscreening Areas Before and After Screening for Advanced and Nonadvanced Cancer in Different Age Groups*

Type of Cancer, by Age Group	Annual Percentage of Change (95% CI), %				Difference in Annual Percentage of Change, *percentage points*†	
	Screening		Nonscreening		Screening	Nonscreening
	Before	After	Before	After		
35–49 y						
Advanced	−1.8 (−3.9 to 0.4)	0.2 (−0.9 to 1.3)	2.0 (0.8 to 3.4)	2.3 (1.7 to 2.8)	2.0	0.3
Nonadvanced	2.5 (0.3 to 4.8)	−1.5 (2.4 to −0.6)	4.3 (3.3 to 5.5)	0.3 (−0.2 to 0.8)	−4.0	−4.0
50–69 y						
Advanced	−0.5 (−1.9 to 0.9)	−1.1 (−1.8 to −0.3)	1.7 (0.8 to 2.6)	3.0 (2.6 to 3.3)	−0.6	1.3
Nonadvanced	4.4 (3.0 to 6.0)	0.6 (0.1 to 1.0)	3.1 (2.2 to 3.9)	1.8 (1.4 to 2.2)	−3.8	−1.3
70–84 y						
Advanced	−0.6 (−2.2 to 1.1)	2.1 (1.3 to 3.0)	1.3 (0 to 2.5)	4.3 (3.8 to 4.8)	2.7	3.0
Nonadvanced	1.7 (−0.1 to 3.7)	2.2 (1.3 to 3.1)	0.5 (−0.4 to 1.7)	3.0 (2.6 to 3.5)	0.5	2.5

* Cancer was defined as advanced if the tumor was >20 mm in diameter and nonadvanced if it was ≤20 mm in diameter.
† Positive values indicate that the incidence increased from the period before screening to that after screening. Negative values indicate that the incidence decreased from the period before screening to that after screening.

period was 1980 to 1990 and the screening period was 1991 to 2010. For Funen, the prescreening period was 1980 to 1993 and the screening period was 1994 to 2010. Similarly, for the areas without screening programs, the "before" period (prescreening period for the control group) was from 1980 to 1990 and the "after" period (screening period for the control group) was from 1991 to 2010, except for women aged 50 to 69 years in which the after period was from 1991 to 2007 (because of the beginning of national rollout).

Association of Screening With Incidence of Advanced Cancer

We used Poisson regression to analyze trends in incidence of advanced and nonadvanced tumors, adjusted for 5-year age groups, and stratified by screening and nonscreening areas. We compared incidence rates (IRs) of nonadvanced and advanced tumors in screening and nonscreening areas and calculated the annual percentage changes before and after screening. In the analysis of women aged 50 to 69 years in the nonscreening areas, we censored data for nonadvanced tumors in 2007 when national screening started. The IR, IR ratios (IRRs), and IR differences with 95% CIs were used to compare rates before and after screening for each age group (35 to 49, 50 to 69, and 70 to 84 years) in screening and nonscreening regions. We used Stata SE, version 14.0 (StataCorp). With Excel, version 14.0 (Microsoft), we produced graphs showing the 3-year moving average incidence of advanced and nonadvanced tumors and marked exact yearly IRs.

Estimating Overdiagnosis

In our first approach, we calculated the IR of advanced and nonadvanced tumors in the before and after periods for nonscreening and screening areas among women aged 50 to 84 years; the number of tumors before and after in the nonscreening and screening areas was calculated by multiplying the IR by the number of women aged 50 to 84 years living in Denmark in 2010. The number of overdiagnosed tumors was the difference between the number of tumors in the screening areas (after − before) and the nonscreening areas (after − before). We estimated overdiagnosis using the number of tumors among nonscreened women not being screened (nonscreening areas; standardized to the Danish population in 2010) in different age groups (50 to 69 and 50 to 84 years) as the denominators. We estimated overdiagnosis of invasive tumors only and invasive tumors and DCIS combined.

This approach accounts for a reduction in the incidence of cancer due to earlier diagnosis in women no longer screened and for increasing incidence trends over time not related to screening. We included the prevalence peak in the screening areas because follow-up after the introduction of screening was longer than 10 years and estimates of the average lead time are 1 to 5 years (15). Thus, we allowed for sufficient follow-up after the first screening round to observe the expected decrease in incidence after an initial peak. (See the Supplement, available at www.annals.org, for the formula and an example.)

In our second approach, we analyzed trends in advanced and nonadvanced cancer in the screening and nonscreening areas among women younger (35 to 49 years) and older (70 to 84 years) than those included in the program and compared these trends with those in women in the screening age range (50 to 69 years). This accounted for regional differences unrelated to screening. We found similar patterns in trends of advanced cancer among women eligible and ineligible for screening. The relative increase of advanced breast tumors was higher in the nonscreening areas than in the screening areas for women aged 35 to 49 years (IRR, 1.61 and 0.78), 50 to 69 years (IRR, 1.46 and 0.96), and 70 to 84 years (IRR, 1.81 and 1.25). We also found no compensatory decrease in the incidence of invasive

cancer in women aged 70 to 84 years who were no longer offered screening. Thus, we concluded that screening was not associated with a reduction in the incidence of advanced cancer and used the incidence increase for nonadvanced tumors in women aged 50 to 69 years to calculate overdiagnosis. (See the **Supplement** for the formula and an example.)

This study was exempt from institutional review board approval.

Role of the Funding Source

This study received no external funding.

RESULTS

In 2010, the Danish population included 1 420 701 women aged 35 to 84 years. The DBCG database included 94 932 women aged 35 to 84 years diagnosed with invasive breast cancer (n = 90 665) or DCIS (n = 4267) from 1980 to 2010, whereas the DCR included data on 105 994 women with invasive tumors and DCIS until 2011. The difference was mostly because of more tumors registered in the period before 1990. The **Supplement Table** shows the number of tumors (advanced and nonadvanced) and person-years in each age group for screening and nonscreening areas.

Incidence of Advanced Cancer

Figure 1 shows trends in the incidence of advanced cancer over time by age group. **Table 1** shows the annual percentage of change before and after screening in screened and nonscreened areas by age group. **Table 2** shows IRs, IR differences, and IRRs for screened and nonscreened areas by age group.

Among women aged 35 to 49 years in nonscreened areas, the incidence of advanced cancer increased throughout the observation period (**Figure 1**, *A*) and was more pronounced after the 2007 rollout of the national program, although this age group was ineligible for screening. The annual percentage of change in incidence was 2.0% (95% CI, 0.8% to 3.4%) before screening and 2.3% (CI, 1.7% to 2.8%) after screening (**Table 1**). The difference in IRR comparing before with after screening was 1.61 (CI, 1.52 to 1.69), and the IR difference was 18.0 (CI, 16.2 to 19.8) per 100 000 person-years (**Table 2**). In contrast, the screening areas had an annual decrease of −1.8% (CI, −3.9% to 0.4%) before screening and an annual increase of 0.2% (CI, −0.9% to 1.3%) after screening (**Table 1**). The difference in IRR before and after screening was 0.78 (CI, 0.71 to 0.86), and the IR difference was −10.1 (CI, −14.2 to −6.1) per 100 000 person-years (**Table 2**).

Among women aged 50 to 69 years in the nonscreening areas, the incidence of advanced cancer increased throughout the observation period (**Figure 1**, *B*). The annual percentage of change in incidence was 1.7% (CI, 0.8% to 2.6%) before screening and 3.0% (CI, 2.6% to 3.3%) after screening (**Table 1**). The difference in IRR before and after screening was 1.46 (CI, 1.41 to 1.52), and the IR difference was 37.8 (CI, 34.4 to 41.5) per 100 000 person-years (**Table 2**). In the screening areas, the trends before and after screening were similar (IRR, 0.96 [CI, 0.90 to 1.02]) (**Table 2**).

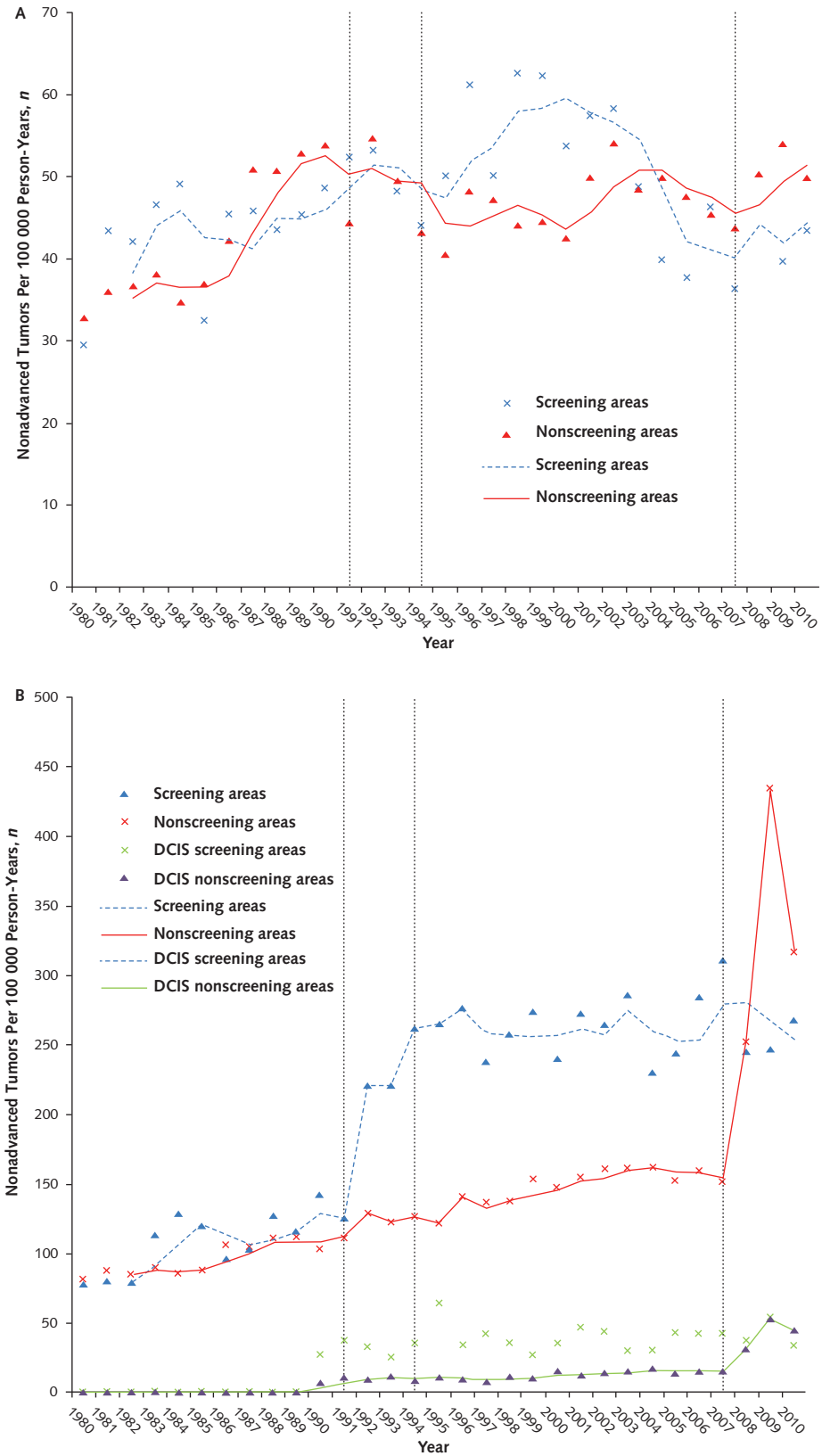
Among women aged 70 to 84 years in the nonscreening areas, the incidence of advanced cancer increased throughout the observation period and was most pronounced in the later years (**Figure 1**, *C*). The difference in IRR before and after screening was 1.81 (CI, 1.72 to 1.90), and the IR difference was 72.5 (CI, 67.0 to 78.0) per 100 000 person-years (**Table 2**). This same pattern was observed among women in the screening areas. Similar to younger women, women aged 70 to 84 years had a difference in IRR before and after screening that was less in the nonscreening areas (1.25 [CI, 1.16 to 1.34]), and their IR difference was 30.8 (CI, 20.7 to 40.9) per 100 000 person-years (**Table 2**).

Table 2. IRs per 100 000 Person-Years of Breast Cancer and IRRs in the Screening and Nonscreening Areas Before and After Screening for Advanced and Nonadvanced Cancer in Different Age Groups*

Type of Cancer, by Age Group	IR per 100 000 Person-Years				Difference (95% CI)†			
	Screening		Nonscreening		Screening		Nonscreening	
	Before	After	Before	After	IRR	IR per 100 000 Person-Years	IRR	IR per 100 000 Person-Years
35–49 y								
Advanced	46.4	36.3	29.7	47.6	0.78 (0.71 to 0.86)	−10.1 (−14.2 to −6.1)	1.61 (1.52 to 1.69)	18.0 (16.2 to 19.8)
Nonadvanced	43.6	49.8	42.6	47.6	1.14 (1.05 to 1.25)	6.2 (2.0 to 10.3)	1.12 (1.07 to 1.17)	5.0 (3.0 to 7.0)
50–69 y								
Advanced	117.0	112.2	82.2	120.1	0.96 (0.90 to 1.02)	−4.8 (−12.1 to 2.4)	1.46 (1.41 to 1.52)	37.8 (34.4 to 41.5)
Nonadvanced	111.4	258.9	95.6	142.0	2.32 (2.20 to 2.46)	147.5 (138.6 to 156.3)	1.49 (1.43 to 1.54)	47.6 (43.8 to 51.4)
70–84 y								
Advanced	124.0	154.8	89.7	162.2	1.25 (1.16 to 1.34)	30.8 (20.7 to 40.9)	1.81 (1.72 to 1.90)	72.5 (67.0 to 78.0)
Nonadvanced	98.6	160.7	102.5	152.5	1.63 (1.51 to 1.76)	62.1 (52.4 to 71.9)	1.49 (1.42 to 1.56)	50.1 (44.4 to 55.7)

IR = incidence rate; IRR = incidence rate ratio.
* Cancer was defined as advanced if the tumor was >20 mm in diameter and nonadvanced if it was ≤20 mm in diameter. The **Supplement Table** (available at www.annals.org) shows the number of tumors and person-years used to calculate IRs.
† An IRR >1.00 indicates that the incidence increased in the period after screening compared with that before screening. An IRR <1.00 indicates that the incidence decreased in this period. A positive IR difference indicates an average annual increase in incidence per 100 000 person-years. A negative IR difference indicates an average annual decrease in incidence per 100 000 person-years.

Figure 2. Three-year moving averages of nonadvanced breast tumors (≤20 mm) in women aged 35 to 49 y (*A*), 50 to 69 y (*B*), and 70 to 84 y (*C*).



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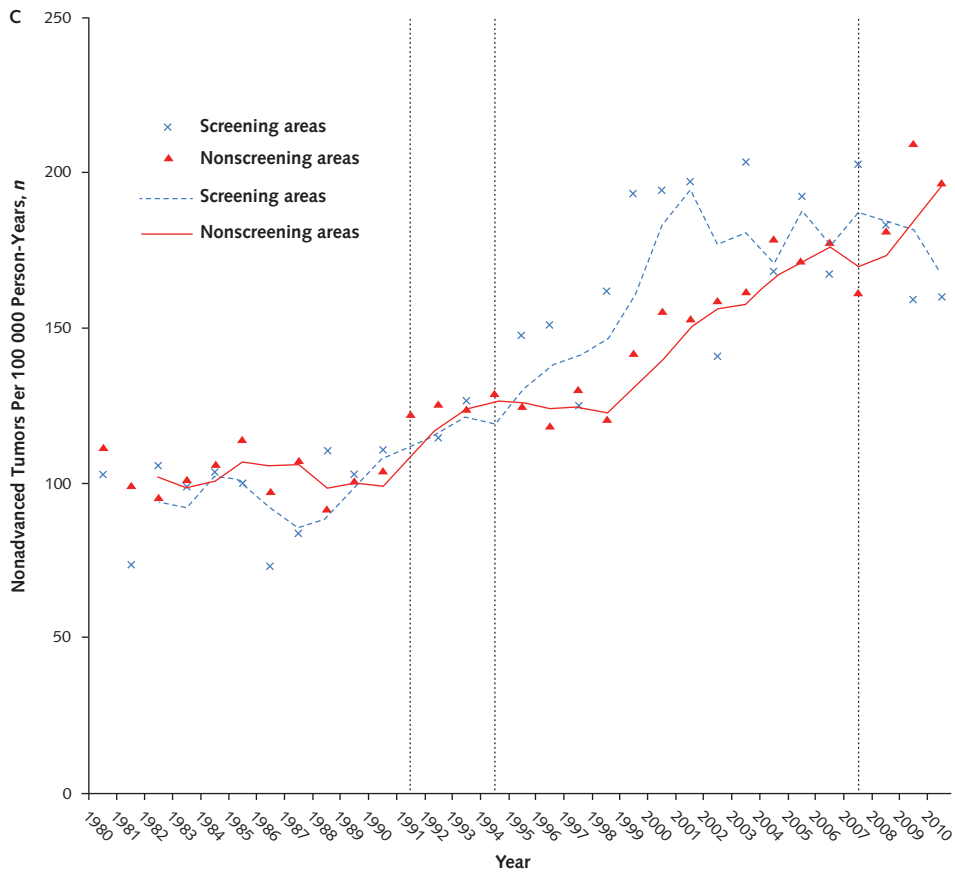

The vertical dotted lines indicate the year of introduction of breast screening in Copenhagen (1991), Funen (1994), and the remaining regions in Denmark (2007). (See **Supplement Figure 5**, available at www.annals.org, for separate incidence rates for Copenhagen and Funen.) DCIS = ductal carcinoma in situ.

Incidence of Nonadvanced Tumors

Among women aged 35 to 49 years in both screening and nonscreening areas, the incidence of nonadvanced tumors increased before screening (**Figure 2**). After screening, no significant change was found in the annual percentage of change in nonscreening areas, but a slight decrease was noted in screening areas (−1.5% [CI, −2.4% to −0.6%]) (**Table 1**). For the nonscreening areas, the difference in IRR comparing before and after screening was 1.12 (CI, 1.07 to 1.17), and the IR difference was 5.0 (CI, 3.0 to 7.0) per 100 000 person-years (**Table 2**). For the screening areas, the difference in IRR before and after screening was 1.14 (CI, 1.05 to 1.25), and the IR difference was 6.2 (CI, 2.0 to 10.3) per 100 000 person-years (**Table 2**).

Among women aged 50 to 69 years before screening, incidence increased similarly in nonscreening and screening areas (**Figure 2**, *B*), with an annual percentage of change of 3.1% (CI, 2.2% to 3.9%) and 4.4% (CI, 3.0% to 6.0%) per 100 000 person-years, respectively (**Table 1**). After screening, the incidence increase in the nonscreening areas diminished (annual increase, 1.8% [CI, 1.4% to 2.2%]) (**Table 1**). In the screening areas, incidence increased abruptly by 140% (prevalence peak) and was followed by a trend of increasing incidence less than that before screening (**Figure 2**, *B*). In the nonscreening areas, the difference in IRR before and after screening was 1.49 (CI, 1.43 to 1.54), and the IR difference was 47.6 (CI, 43.8 to 51.4) per 100 000 person-years. But in the screening areas, the difference in IRR was 2.32 (CI, 2.20 to 2.46), and the IR difference was 147.5 (CI, 138.8 to 156.3) per 100 000 person-years (**Table 2**). The IR in the nonscreening areas, which initiated the screening program in late 2007, increased substantially from 2009 to 2011, but the follow-up is too short to assess whether it will stabilize.

Among women aged 70 to 84 years, incidence of nonadvanced cancer increased similarly in the screening and nonscreening areas, and the relative change was slightly greater in the screening than in the nonscreening areas (**Figure 2**, *B*). In the nonscreening areas, the difference in IRR before and after screening was 1.49 (CI, 1.42 to 1.56), and the IR difference was 50.1 (CI, 44.4 to 55.7) per 100 000 person-years (**Table 2**). In the screening areas, the corresponding values were 1.63 (CI, 1.50 to 1.76) and 62.1 (CI, 52.4 to 71.9), respectively (**Table 2**).

Table 3. IRs per 100 000 Person-Years Among Women Aged 50 to 84 y (Approach 1) and 50 to 69 y (Approach 2) in Different Areas Before and After Screening, by Type of Cancer*

Variable	Before		After		Difference in Tumors, *n*	Overdiagnosed Tumors, *n*
	IR per 100 000 Person-Years	Tumors, *n*	IR per 100 000 Person-Years	Tumors, *n*		
Screening						
Advanced	119.8	1171	127.3	1244	73	–
Nonadvanced	106.3	1038	224.0	2189	1151	–
Nonscreening						
Advanced	84.6	826	134.4	1313	487	–
Nonadvanced	97.8	956	145.6	1422	466	–
Approach 1	–	–	–	–	–	271†
Nonadvanced in screening areas	111.4	783	258.9	1821	1038	–
Nonadvanced in nonscreening areas	95.6	672	142.0	999	327	–
Approach 2	–	–	–	–	–	711‡

IR = incidence rate.
* Cancer was defined as advanced if the tumor was >20 mm in diameter and nonadvanced if it was ≤20 mm in diameter. The number of tumors were estimated according to the Danish female population aged 50 to 84 y (977 006 women) and 50 to 69 y (703 289 women) (IR × population/100 000). The number of overdiagnosed tumors in approach 1 includes both advanced and nonadvanced tumors, whereas approach 2 includes only nonadvanced tumors. Both approaches estimate the number of overdiagnosed tumors as the difference between the number of tumors in the screening areas and that in the nonscreening areas before and after screening.
† (73 + 1151) − (487 + 466).
‡ 1038 − 327.

DCIS

Screening was associated with a pronounced and sustained increase in incidence of DCIS (Figure 2, *B*). In the screening areas, average incidence was 38.2 per 100 000 person-years, with a constant rate between 1991 and 2007. However, in the nonscreening areas, it increased from 10 to 15 per 100 000 person-years from 1991 to 2007. After 2007, the incidence of DCIS was similar throughout Denmark.

Table 3 shows the IR of advanced and nonadvanced tumors in the screening and nonscreening areas, corresponding absolute number of tumors detected, and estimates of overdiagnosed tumors. Table 4 shows the absolute number and corresponding percentages of overdiagnosed tumors (with and without DCIS).

Our data show that the introduction of breast cancer screening was not associated with reduced rates of advanced cancer when we accounted for incidence trends in women younger than the screening age. The introduction of breast screening was clearly associated with increased rates of nonadvanced breast tumors and DCIS, which were not compensated for by a decrease in incidence in women no longer invited to screening. (See Supplement Figures 4 and 5 for data about Copenhagen, Frederiksberg, and Funen separately.)

Overdiagnosis

First Approach

Standardized to the 2010 female population in Denmark, 271 invasive breast tumors and 180 cases of DCIS were overdiagnosed each year, and 1844 tumors were detected in nonscreening areas in women aged 50 to 69 years. Table 3 shows the IRs, number of advanced and nonadvanced tumors standardized to the 2010 female Danish population in screening and nonscreening areas, and the corresponding number of overdiagnosed tumors. Table 4 shows the number of overdiagnosed tumors, including DCIS, with the corresponding percentages of overdiagnosis. The amount of overdiagnosis was 24.4% when DCIS was included and 14.7% for invasive tumors only compared with the incidence observed in women aged 50 to 69 years in nonscreening areas (Table 4). Therefore, 1 in every 5 women aged 50 to 69 years diagnosed with breast cancer was overdiagnosed in the screening areas.

Including women aged 70 to 84 years in the denominator diminished the estimated percentages because the difference was diluted. Among women aged 50 to 84 years in 2010, the percentage estimate of overdiagnosis decreased to 16.4% for invasive tumors and DCIS combined and 9.9% for invasive tumors alone (Table 4). The absolute number of overdiagnosed tumors was the same.

Second Approach

Because advanced tumors did not decrease in the screening areas when incidence trends among women aged 35 to 49 years were accounted for, we limited our analysis in the second approach to nonadvanced tumors. Likewise, when incidence trends among younger and older women were compared, there was no clear compensatory decrease in the incidence of advanced tumors in older women, so no adjustment was necessary. Thus, overdiagnosis was calculated as the average incidence of nonadvanced tumors in the screening areas (258.9 per 100 000 person-years) for the after period, minus the average incidence in the before period (111.4 per 100 000 person-years). We then subtracted the average incidence of nonadvanced tumors in the nonscreening areas (142 per 100 000 person-years) for

the after period, minus the average incidence in the before period (95.6 per 100 000 person-years) (Table 2). We included the difference in incidence of DCIS between screening and nonscreening areas (38.2 and 12.4 per 100 000 person-years, respectively; a difference of 25.8 per 100 000 person-years). This provided an estimate of 121.4 overdiagnosed tumors per 100 000 person-years and 95.6 overdiagnosed tumors per 100 000 person-years when DCIS was excluded. The average incidence (nonadvanced and advanced tumors) in the nonscreening areas during the screening period was 262.1 per 100 000 person-years. When standardized to the 2010 population, 711 invasive tumors and 180 cases of DCIS were overdiagnosed each year and 1844 tumors were detected. We thus calculated overdiagnosis rates of 38.6% when excluding DCIS and 48.3% when including DCIS (Table 4). Accordingly, 1 in every 3 women aged 50 to 69 years diagnosed with breast cancer was overdiagnosed in the screening areas.

If we assume no background increase in incidence over time, and include all cases of DCIS (38.2 per 100 000 person-years) based on the observation that their detection was not followed by a decrease in the rates of invasive breast tumors, an even more radical estimate of overdiagnosis could be calculated using the historical rate as the expected rate.

DISCUSSION

Seventeen years of organized breast screening in Denmark has not measurably reduced the incidence of advanced tumors but has markedly increased the incidence of nonadvanced tumors and DCIS. Because of the long follow-up, differential access to screening, and clear increases in the incidence of DCIS and nonadvanced tumors after the introduction of screening, a reduction in incidence of advanced tumors would be expected, even if screening led to an initial increase in incidence of advanced tumors. These findings raise questions about whether screening provides the promised benefits of reduced breast cancer mortality, less invasive treatment, and reduced disease burden. Further, we found evidence for substantial overdiagnosis.

The incidence of advanced tumors was probably influenced by regional differences unrelated to screening. Although the largest decrease in the incidence of advanced tumors was observed in the screening areas, the relative decrease was most pronounced in women younger than the screening age and therefore probably not caused by screening. This finding complicates interpretation and differentiation between factors not related to screening, such as increased awareness, and screening itself. It also underlines the importance of looking at data from women outside the screened age group, which are often not considered (16).

When overdiagnosis was expressed as a relative risk, we estimated an overdiagnosis rate of 24.4% for invasive breast tumors and DCIS combined and 14.7% for invasive breast tumors only. These estimates did not account for the observation that the relative decrease in advanced cancer rates was similar in screening-eligible and screening-ineligible age groups. When our approach accounted for regional differences in women younger than the screening age, our estimate of overdiagnosis (including DCIS) was 48.3%. Therefore, 1 in every 3 breast tumors detected in women aged 50 to 69 years was probably overdiagnosed. Incidence seemed stable when younger age groups were used as a reference for the underlying trends in the incidence of breast cancer without screening. Thus, the incidence in the historical control group could be used as a reference, and the amount of overdiagnosis would then have been higher. Because our first approach did not account for regional differences in incidence trends in women younger than the screening age, we consider the second approach preferable (Supplement Figures 1 and 2).

To our knowledge, our study has the longest follow-up after the start of breast cancer screening. It also has a contemporaneous control group within the same country. Because of the national rollout, further follow-up would not provide more reliable estimates. Yet, several limitations warrant mention.

First, although DCR data are among the most complete in the world, poor registration of cases of DCIS before 2008 caused uncertainty in estimates of overdiagnosis that include DCIS. In addition, because the incidence of DCIS is comparatively low in Denmark, this may lead to an underestimation of overdiagnosis compared with countries with higher rates. Second, screening outside the program is unusual, but exact rates have not been reported (13). Consequently, trends

Table 4. Overdiagnosis in 2010 According to the Average Incidence Method*

Approach, by Age Group	Tumors, *n*			Overdiagnosis, %	
	Overdiagnosed, Including DCIS	Overdiagnosed Invasive Cancer	Without Screening	Including DCIS	Invasive
50–69 y					
Approach 1	450	271	1844	24.4	14.7
Approach 2	891	711	–	48.3	38.6
50–84 y					
Approach 1	450	271	2735	16.4	9.9
Approach 2	891	711	–	32.6	26.0

DCIS = ductal carcinoma in situ.
* See the Supplement (available at www.annals.org) for the formula and calculated examples for approaches 1 and 2.

among noninvited age groups and in nonscreening areas mainly reflect awareness, changes in risk factors, and more sensitive equipment. The average tumor diameter in Denmark decreased by 1 cm from the late 1970s to the early 1980s, long before any screening, which indicates that factors other than screening can be important (17). Third, we examined the incidence of late-stage tumors but not disease-specific mortality. Yet, use of late-stage tumors avoids problems with reliably establishing the cause of death, which, depending on the direction of bias, is sometimes called either "sticky diagnosis bias" or "slippery linkage bias" (18).

Our estimates of overdiagnosis varied between 9.9% and 48.3%, which reflects whether the estimate included DCIS, which age groups were included in the denominator, and whether trends in women too young to be screened were accounted for. Cases of DCIS must be included in estimates of overdiagnosis whenever possible, and the choice of age group and denominator are widely known to influence percentage estimates of overdiagnosis (19). In our estimates of overdiagnosis, which included DCIS and used women aged 50 to 69 years as the denominator, relative risks varied from 24.4% (first approach) to 48.3% (second approach). With the first approach, both nonadvanced and advanced tumors were included, trends in incidence were not interpreted but were rather observed averages, and incidence among younger women was not considered. In the second approach, trends in incidence for nonadvanced and advanced tumors, and for different age groups that included women too young to be screened, were incorporated into the estimate. The main assumption is that trends in stage, differences among age groups, and trends in nonscreening areas must be interpreted and accounted for to understand what the incidence would have been without screening. Cohort studies of trends seem the most appropriate option for estimating overdiagnosis (20).

Both of our approaches to estimate overdiagnosis account for underlying trends in incidence without screening in the screened age groups and have a long follow-up. This allows for observation of a possible compensatory drop among women no longer screened. Since 2007, almost all Danish women aged 70 to 84 years in the screening areas have previously been invited at least once to participate in screening, but we could not identify a compensatory decrease. Supplement Figure 3 depicts a cohort of women who were followed for 5 years before they were offered screening, during 10 years of screening, and for 10 years after they were offered screening. These women were compared with an age-matched contemporary cohort of women not offered screening. Once again, we could not identify a compensatory decrease.

The considerable variation in estimates between studies on overdiagnosis is partly due to variation in the adjustment for lead time and different lengths of follow-up after screening, which means that percentage estimates are incomparable and essentially uninformative. When health care interventions at the population level were compared, estimates of overdiagnosis as percentage increases in the total incidence of overdiagnosis for the screened age groups are more useful. However, overdiagnosis as the percentage of all tumors detected at screening is more informative for women considering screening.

Other studies also show that screening mammography increases the incidence of DCIS and small invasive breast tumors but does not reduce the incidence of advanced breast cancer (3, 4, 7, 8). A review of data from the United States, Europe, and Australia found that the IR of tumors larger than 20 mm was not reduced by screening (3). A study from Norway with a contemporary control group of nonscreened women reported a decreased incidence of stage 3 and 4 tumors of 24% in both screening and nonscreening areas (7). This finding was confirmed in another study (8). Although a U.S. study reported an 8% decrease in regional and distant metastasis over 30 years, it had no contemporary control group of nonscreened women and thus the decrease could have been due to factors other than screening (21).

Our estimates of overdiagnosis are similar to previous estimates (7, 22, 23) from studies with shorter follow-ups that did not consider tumor size. Denmark has lower attendance and fewer recalls than many other countries, which was indicated by the low incidence of DCIS compared with that found in the National Health Service Breast Screening Programme and Norway (24, 25). A literature review from the Euroscreen Working Group concluded that screening mammography had an overdiagnosis rate of 1% to 10%. However, the review included strong model assumptions about cancer growth patterns rather than observational data, excluded DCIS, and used calculations that included women in the denominator who were much older than those screened (26) (Table 4).

Over 17 years, detection of DCIS through screening did not reduce the incidence of invasive breast tumors, which continued to rise, also in regions with screening. In the United Kingdom, 20% of screen-detected lesions are DCIS and this percentage is increasing. But the IR of invasive tumors (24) is also increasing, which suggests that cases of DCIS are usually not precancerous and contribute substantially to overdiagnosis. Our findings validate the importance of trials on DCIS treatment, such as the LORIS (Low-Risk DCIS Trial) trial on immediate treatment versus active monitoring of low-risk DCIS (27).

Breast screening is associated with a substantial increase in the incidence of nonadvanced tumors and DCIS in Denmark but not with a reduction in the incidence of advanced tumors, and the overdiagnosis rate is substantial. These findings support that screening has not accomplished the promise of a reduction in invasive therapy or disease-specific mortality (6, 28–30).

From Nordic Cochrane Centre, Copenhagen, Denmark; and University of Oslo and Norwegian Institute of Public Health, Oslo, Norway.

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Requests for Single Reprints: Karsten Juhl Jørgensen, MD, DrMedSci, The Nordic Cochrane Centre, Rigshospitalet, Department 7811, Blegdamsvej 9, DK-2100 Copenhagen, Denmark; e-mail, kj@cochrane.dk.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Jørgensen and Gøtzsche: The Nordic Cochrane Centre, Rigshospitalet, Department 7811, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
Dr. Kalager: University of Oslo, Institute of Health and Society, Department of Health Management and Health Economics, PO Box 1089, Blindern, 0318 Oslo, Norway.
Dr. Zahl: Norwegian Institute of Public Health, PO Box 4404, Nydalen, N-0403 Oslo, Norway.

Author Contributions: Conception and design: K.J. Jørgensen, P.C. Gøtzsche, M. Kalager, P.H. Zahl.
Analysis and interpretation of the data: K.J. Jørgensen, P.C. Gøtzsche, M. Kalager, P.H. Zahl.
Drafting of the article: K.J. Jørgensen, M. Kalager, P.H. Zahl.
Critical revision of the article for important intellectual content: K.J. Jørgensen, P.C. Gøtzsche, M. Kalager, P.H. Zahl.
Final approval of the article: K.J. Jørgensen, P.C. Gøtzsche, M. Kalager, P.H. Zahl.
Statistical expertise: K.J. Jørgensen, M. Kalager, P.H. Zahl.
Administrative, technical, or logistic support: P.C. Gøtzsche.
Collection and assembly of data: P.H. Zahl.