European Journal of Cancer 89 (2018) 102–112

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

No overdiagnosis in the Norwegian Breast Cancer Screening Program estimated by combining record linkage and questionnaire information in the Norwegian Women and Cancer study

Eiliv Lund [a,*], Aurelie Nakamura [a], Jean-Christophe Thalabard [b]

[a] *Institute of Community Medicine, UiT the Artic University of Norway, Tromso, Norway*
[b] *MAP5, Université Paris Descartes, Paris, France*

Received 15 September 2017; received in revised form 25 October 2017; accepted 2 November 2017
Available online 12 December 2017

KEYWORDS
Overdiagnosis;
Breast cancer;
The Norwegian Breast Cancer Screening Program;
The Norwegian Women and Cancer study;
NOWAC

Abstract ***Background:*** The Norwegian Breast Cancer Screening Program (NBCSP) was implemented across the country in 2005 and has been criticised for potential 'overdiagnosis', i.e. a breast cancer diagnosis that otherwise would not have been detected or treated in a woman's lifetime. We aimed to estimate overdiagnosis in the NBCSP based on the Norwegian Women and Cancer (NOWAC) study using both questionnaire information and record linkage information from NBCSP.

Method: For 124,978 women aged 49–79 years from the NOWAC study, information on *screened* women could be cross-validated from the NBCSP database. Based on information from the NOWAC questionnaire, *unscreened women* were further divided into those who had *mammograms taken only outside the NBCSP* and those who had *never had taken a mammogram*. Breast cancers diagnosed in 2005–2013 were identified through linkage to the Cancer Registry of Norway; *in situ or DCIS* 417; invasive 2845; combined 3262. Cumulative incidence rates (CIRs) for ages 49–79 years of breast cancer were compared using the log-rank test.

Results: After exclusion of women with a family history of breast cancer, screened women had a CIR of 9.7% for combined breast cancer, non-significantly lower compared with unscreened women. Screened women had a 1.1% increased CIR or 13.0% increased relative risk of breast cancer diagnosis (significant) compared with women who had never had a mammogram, but for invasive breast cancer alone the difference was reduced to −0.2% (95% CI: −9.1; 8.8). Invasive breast cancers were significantly smaller (<2.5 cm) in screened versus unscreened

* *Corresponding author.*
E-mail addresses: eiliv.lund@uit.no (E. Lund), aurelienakamura@gmail.com (A. Nakamura), jean-christophe.thalabard@mi.parisdescartes.fr (J.-C. Thalabard).

https://doi.org/10.1016/j.ejca.2017.11.003

women. There was a borderline significant decrease in lymph node positive cancer among screened (p = 0.06).
Conclusion: The findings of no significant overdiagnosis combined with smaller tumours and less lymph node metastases suggest that the prevailing view of overdiagnosis in the NBCSP should be challenged.

1. Background

Recently, concerns about the side-effects of national breast cancer screening programs have increased [1], including concerns about potential overdiagnosis. Overdiagnosis is defined as a cancer diagnosis that is a result of screening and that would not have been detected in the woman's lifetime if screening had not taken place. The amount and severity of overdiagnosis is heavily debated [2–4]. Several reviews and meta-analyses have been published over the last few years. An independent meta-analysis of three early clinical trials reported a 19% increased incidence of breast cancer among screened women in the target screening population (50–69 years), which decreased to 11% when women older than the screening age limit were included [2]. These figures were more dramatic in a 2013 Cochrane review, which reported an estimated overdiagnosis and overtreatment of 30% [3]. However, the 2014 balance sheet from the EUROSCREEN working group showed that women screened biennially from 50 to 69 years of age and then followed up for breast cancer incidence until 79 years of age had only four overdiagnosed cases out of 1000 screened women [4]. The recent International Agency for Research on Cancer monograph reported overdiagnosis estimates of 15–25% [5] similar to the estimates generated for the Norwegian Breast Cancer Screening Program (NBCSP) as part of an evaluation made by the Research Council of Norway [6]. An ecological analysis from the SEER registries in the United States reported even higher estimates [7]. In a recent systematic review published as part of the development of the American Cancer Association guidelines [8], the conclusion was that there is large uncertainty about the magnitude of overdiagnosis associated with different screening strategies. The same uncertainty of the estimates was expressed in a recent review [9].

The potential for ecological fallacy attributable to the extensive use of grouped data, e.g. geography as a proxy for screening attendance, has often been neglected, and resultant associations interpreted as causal. The rapid increase and decrease of hormone replacement therapy (HRT) use around year 2000 could also add to the uncertainty of ecological analyses, as HRT reduces the sensitivity and specificity of mammography [10]. In addition, most women with a family history of breast cancer are under specific surveillance outside of national screening programs; this is the case for a substantial portion of women with a family history of breast cancer in Norway [11]. As these women are followed regularly outside the NBCSP, they should not be included in analyses of overdiagnosis as unscreened. However, estimates of overdiagnosis *should* reflect the two different subgroups among unscreened women, as in reality, many unscreened women undergo opportunistic screening or wild screening outside national screening programs. Thus the best and most accurate reference group should consist of women who have *never* had a mammogram. Analyses of overdiagnosis should also take into consideration that *in situ* diagnoses are generally based on mammographic information, not clinical examination, and that mammographic diagnoses of *in situ* cancer are an expected effect of screening. Indeed, such diagnoses allow for the detection and removal of lesions before they progress to invasive cancer. The progression rate to invasive breast cancer is unknown, but early removal of *in situ* lesions should reduce later incidence of invasive breast cancer [12].

The aim of this analysis was to determine the presence of overdiagnosis in the NBCSP during its first 9 years of national coverage (2005–2013) based on information from the Norwegian Women and Cancer (NOWAC) study, one of the few studies with information on mammograms performed within and outside a national breast cancer screening program.

2. Methods

2.1. The Norwegian Breast Cancer Screening Program

The NBCSP started in 1996 in four Norwegian counties as a pilot program and was fully implemented across the country early in 2005. Women aged 50–69 years are invited to be screened by digital mammography within the NBCSP every other year. At the start of the study period (2005), prevalence screening had just been completed in the last two counties. Consequently, in the study period all women were first invited or screened at age 50 to 51.

2.2. Study population—the Norwegian Women and Cancer study

The NOWAC study is a national population-based cohort study which started in 1991 [13]. A random sample of Norwegian women (n = 172 748) filled in one to three questionnaires during the period 1991 to 2013. NOWAC participants who were aged 49 to 79 during the first 9 years of national coverage of the NBCSP (2005–2013) were selected for the present analysis. We included women living in Norway with no previous cancer diagnosis. In this analysis, the dates of NBCSP mammograms were taken from the NBCSP database through a linkage to NBCSP by the use of thee unique national identifier or Norwegian personal number. Information on non-NBCSP mammograms was taken from the NOWAC questionnaires. The NOWAC questionnaires contained information on reproductive and lifestyle factors, including maternal history of breast cancer. Table 1 shows those that will be used for adjustment as risk factors.

Death and emigration status were extracted from the Cause of Death Registry and the Central Population Registry at Statistics Norway. Cases of invasive and *in situ* breast cancer were identified through linkage to the Cancer Registry of Norway using the unique national identifier or Norwegian personal number. The 124 978 women included in the analyses contributed 1 002 613 person-years at risk during the study period (2005–2013). Study entry was defined as 1 January 2005 or the date of the first questionnaire answered after that date. Study exit was defined as the date of cancer diagnosis, emigration, death, or the end of 2013, whichever occurred first.

The external validity was considered by comparing the cumulative incidence rate curves for invasive breast cancer in the NOWAC cohort with those published by the Cancer Registry of Norway [14] for the period 2007 to 2013 in Fig. 1. The cumulative incidence rate were non-significantly increased in the NOWAC study (log-rank test, p = 0.30).

Table 1
Characteristics of the study sample from the Norwegian Women and Cancer cohort. The percentage number of women in each group (screened within the Norwegian Breast Cancer Screening Program (NBCSP), mammogram taken only outside the NBCSP, and never had a mammogram) corresponds to the year 2005.

Characeristics	Screened	Outside	Never
N	83,963	31,041	9974
Age	N = 83,938	N = 31,041	N = 9,974
48–52	10.5	68.0	73.5
53–59	56.0	18.8	10.8
60–69	30.1	7.4	5.4
70–84	3.4	5.8	10.4
Mother hist. of BC			
Yes	5.4	6.8	2.5
No	94.6	92.2	97.6
Parity			
0	8.1	10.3	10.0
1–2	52.8	55.7	49.8
2–3	35.7	31.5	35.6
5+	3.4	2.4	4.6
Menopausal status			
Postmenopausal	91.9	51.2	44.4
Premenopausal	8.1	48.8	55.6
Current use of HRT			
Yes	18.6	14.4	7.3
No	81.4	85.6	92.7
BMI	N = 80,798	N = 30,154	N = 9,396
<25	52.1	57.4	5670
25+	47.9	42.6	43.0

Abbreviations: BC, breast cancer; BMI, body mass index; HRT, hormone replacement therapy.

2.3. Statistical analyses

Women were categorised as *unscreened* until their first NBCSP mammogram, at which they were moved to the *screened* category. This was taken into account in the person-year calculation. However, once a woman was classified as screened, she remained in the screened group, even if she received a non-NBCSP mammogram later. This was due to the lack of repeated questionnaires and national registers on mammograms taken outside the NBCSP. *Unscreened* women consisted of two sub-cohorts; women with *non-NBCSP mammograms* only had an outside mammogram at time of recruitment, and women who had *never taken* a mammogram at time of recruitment. Analyses of the different groups in relation to breast cancer incidence (*in situ* and

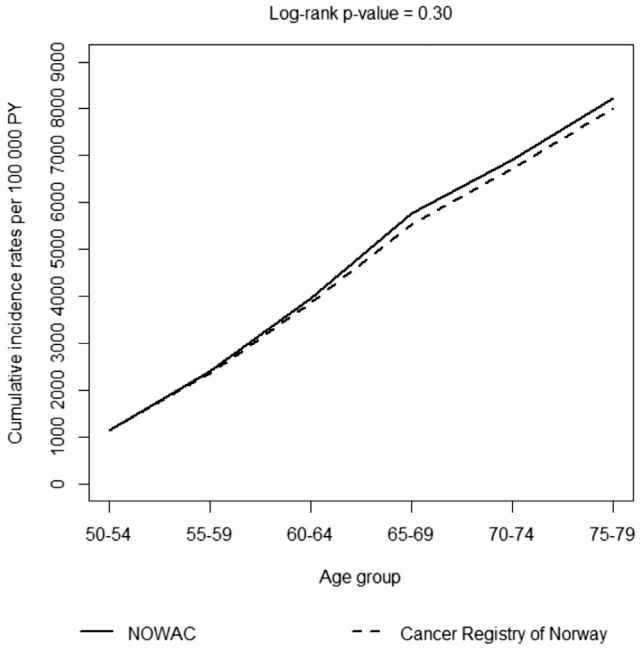

Fig. 1. Cumulative incidence rates for women participating in NOWAC and national figures from the Cancer Registry of Norway, 2009–2011. NOWAC, Norwegian Women and Cancer study.

invasive), tumour size (small < 2.5 cm, large 2.5), and lymph node status (yes/no) were performed based on information from the Norwegian Cancer Registry.

Statistical analyses were run using SAS 9.4 (SAS Institute, Cary NC, USA). We chose to divide age into seven groups (49–52, 53–55, 56–59, 60–64, 65–69, 70–74, 75–79 years). The prevalence group was defined as women who had their first NBSCP mammogram between 49 and 52 years of age, since some women were invited to the NBCSP for the first time at 52 years of age. Cumulative breast cancer incidence rates were calculated by summing the age-specific breast cancer incidence rates [15]. The breast cancer incidence rate for an age group was calculated as the number of new breast cancer cases during the period 2005–2013 divided by the number of women at risk during the same period. Rates were reported per 100 000 person-years. Cumulative breast cancer incidence rates across all age groups combined were compared between the groups using log-rank tests. Two groups were regarded as statistically significantly different if a two-sided Chi-squared test p-value was less than 0.05. Hazard ratios and 95% CIs were obtained using Cox regression. Age was used as the time-scale. Multivariate analyses were adjusted for parity (0, 1–2, 3–4, 5 + children), menopausal status (premenopausal, postmenopausal), current HRT use (yes, no) and body mass index (<25, 25+) as given in the questionnaire at the start of follow-up.

3. Results

Characteristics of the study population are given in Table 1. The participants who never had a mammogram group consisted of 9974 women out of a total of 124,978 women. They had less family history of breast cancer and less use of current HRT than women with a mammogram. During the study period, 3262 cases of breast cancer were identified in the Cancer Registry of Norway: 417 (12.8%) cases of *in situ* breast cancer and 2845 (87.2%) cases of invasive breast cancer. *In situ* breast cancer made up 13.2% of all breast cancers among screened women and 9.8% in unscreened women. Thus, the breast cancer incidence rate for *in situ* breast cancer was 42 per 100 000 person-years and 284 per 100 000 person-years for invasive breast cancer. For validation purposes, we compared the NOWAC questionnaire information and the information on NBCSP mammograms in the NBCSP database in a sample of 11 463 NOWAC participants aged 50 years or older. The results showed that only 1.7% of the 8214 women who participated in the NBCSP denied their participation.

3.1. Screened versus unscreened women

The age-specific incidence rates of invasive breast cancer for screened and unscreened women are given in Fig. 2.

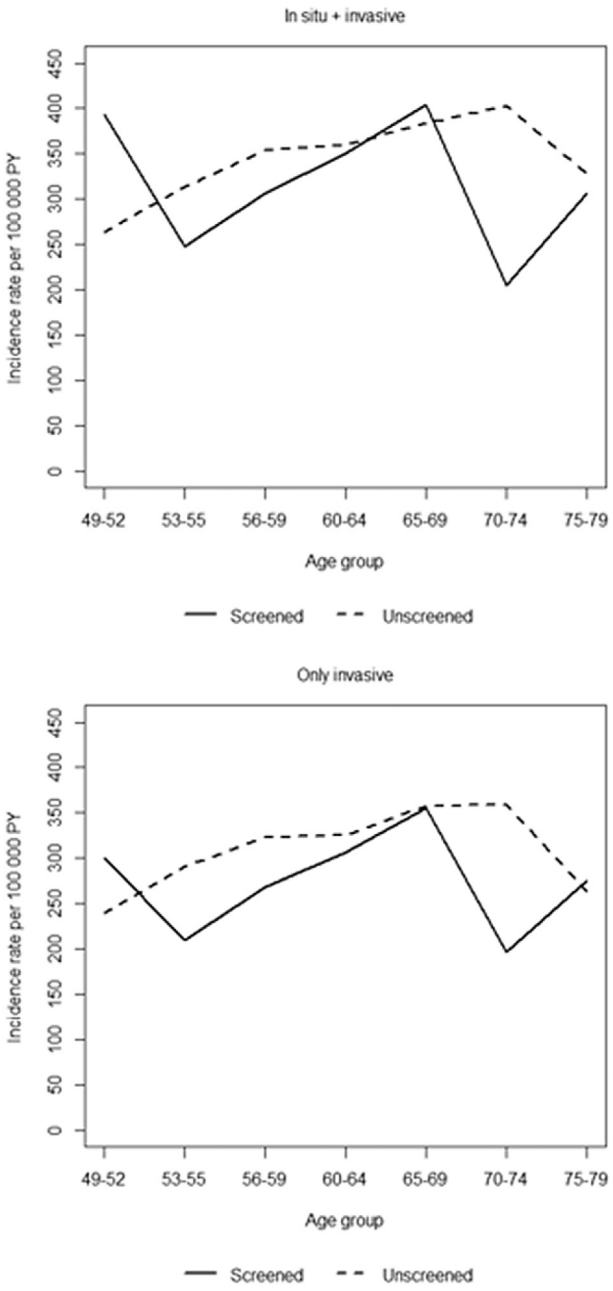

Fig. 2. Age-specific breast cancer incidence rates per 100 000 person-years for screened and unscreened women: *in situ* and invasive combined and invasive alone, the Norwegian Women and Cancer cohort, 2005–2013.

Prevalence screening in Norway is directed at women aged 49–52 years and corresponded with an increased risk of breast cancer diagnosis for screened women versus unscreened women (RR = 1.49; 95% CI 1.18–1.88). In the other age groups, incidence rates in unscreened women were slightly higher than those in screened women. The incidence rates dropped among screened women who were over the target screening age and thus no longer invited to the NBCSP, i.e. 70 years of age and over, but rates continued to grow for the

unscreened group (screened versus unscreened groups: RR = 0.51; 95% CI 0.30–0.85). However, 5 years after women left the NBCSP, an inverse trend was observed in the incidence rates for screened and unscreened women, converging to around 300 cases per 100 000 person-years (RR = 0.93; 95% CI 0.61–1.44).

In an analysis combining *in situ* and invasive breast cancer, unscreened women had a CIR of 10.8% compared with 9.9% for screened women i.e. a difference of 0.92% (Table 2). A Cox regression analysis comparing unscreened women to screened women showed an 8% non-significant increased risk (RR = 1.08; 95% CI 0.96–1.22) without adjustment and a 4% non-significant increased risk after adjustment for cofactors (RR = 1.04; 95% CI 0.92–1.18).

3.2. Family history of breast cancer

For the sub-cohort of women with a maternal history of breast cancer, the cumulative incidence rates for all cancers were 13.8% for screened versus 21.1% for unscreened women (log-rank test, $p < 0.001$; data not shown). After removing women with a maternal history of breast cancer from the screened and unscreened groups, the difference in cumulative incidence rates became smaller (Table 2 and Fig. 3), 9.7% versus

Table 2
Number of breast cancer cases among study women by maternal history of breast cancer, screening status, age, person-years and incidence rates, and cumulative incidence rates per 100 000 person-years, the Norwegian Women and Cancer cohort, 2005–2013.

All women		49–52	53–55	56–59	60–64	65–69	70–74	75–79	Cumulative rates %
Screened	Cases	152	325	719	952	578	77	49	
	PY	38,693	130,880	234,922	271,073	142,982	37,511	16,012	
	Rate	393	248	306	351	404	205	306	9.9
Unscreened	Cases	140	55	70	61	30	18	36	
	PY	53,024	17,519	19,786	16,942	7817	4462	10,992	
	Rate	264	314	354	360	384	403	328	10.8
Only women without mother history of breast cancer									
Screened	Cases	143	305	660	870	533	72	46	
	PY	36,987	124,623	222,831	256,185	135,134	35,621	15,209	
	Rate	387	245	296	340	394	202	302	9.7
In situ	Cases	36	46	84	109	63	3	4	
	PY	36,987	124,623	222,831	256,185	135,134	35,621	15,209	
	Rate	97	37	38	43	47	8	26	1.3
Invasive	Cases	107	259	576	761	470	69	42	
	PY	36,987	124,623	222,831	256,185	135,134	35,621	15,209	
	Rate	289	208	258	297	348	194	276	8.4
Unscreened	Cases	123	46	63	50	28	15	34	
	PY	50,157	16,064	18,015	15,480	7202	4266	10,541	
	Rate	245	286	350	323	389	352	323	10.2
In situ	Cases	10	4	4	6	2	2	6	
	PY	50,157	16,064	18,015	15,480	7202	4266	10,541	
	Rate	20	25	22	39	28	47	57	1.1
Invasive	Cases	113	42	59	44	26	13	28	
	PY	50,157	16,064	18,015	15,480	7202	4266	10,541	
	Rate	225	261	328	284	361	305	266	9.1
Only outside	Cases	102	39	55	42	22	9	24	
	PY	36,159	12,064	13,818	12,033	5332	3085	6869	
	Rate	282	323	398	349	413	292	349	10.7
In situ	Cases	10	4	4	6	2	2	6	
	PY	36,159	12,064	13,818	12,033	5332	3085	6869	
	Rate	28	33	29	50	38	65	87	1.5
Invasive	Cases	92	35	51	36	20	7	18	
	PY	36,159	12,064	13,818	12,033	5332	3085	6869	
	Rate	254	290	369	299	375	227	262	9.2
Never taken a mammogram	Cases	21	7	8	8	6	6	10	
	PY	13,997	4000	4198	3447	1870	1181	3673	
	Rate	150	175	191	232	321	508	272	8.6
In situ	Cases	0	0	0	0	0	0	0	
	PY	13,997	4000	4198	3447	1870	1181	3673	
	Rate	0	0	0	0	0	0	0	0.00
Invasive	Cases	21	7	8	8	6	6	10	
	PY	13,997	4000	4198	3447	1870	1181	3673	
	Rate	150	175	191	232	321	508	272	8.6

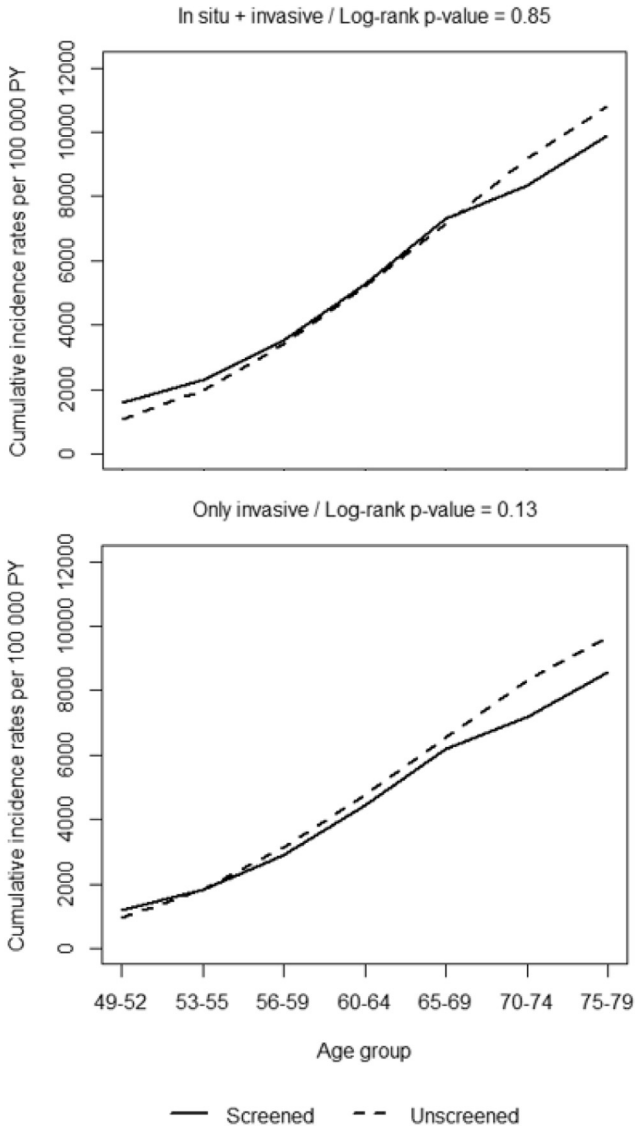

Fig. 3. Cumulative breast cancer incidence rates per 100 000 person-years according to screening status, *in situ* and invasive combined and invasive alone, the Norwegian Women and Cancer cohort, 2005–2013.

10.17%. Further restricting the analysis to only invasive breast cancer indicated a larger difference (p = 0.13; Fig. 3). The cumulative incidence rates for *in situ* breast cancer were almost equal among screened and unscreened women, 1.3% versus 1.10% (Table 2).

3.3. Women with mammograms taken only outside NBCSP versus women who never had a mammogram

Subgroup analyses comparing women with non-NBCSP mammograms to women who had never had a mammogram showed a higher CIR (*in situ* and invasive breast cancer combined) of 10.7% in the former group and 8.6% in the latter group (Table 2). Most of this difference was due to the lack of *in* situ among women who never had a mammogram. The group of women who never had a mammogram had not one single diagnosis of *in situ*.

3.4. Screened women versus those who never had a mammogram

Combining *in situ* and invasive breast cancer in a comparison between screened and never-taken-a-mammogram women yielded a difference in cumulative incidence rate of 1.1% or a relative difference of 13.0% ($p < 0.01$), Fig. 4. The cumulative incidence rate became non-significant when restricted to invasive breast cancer only; difference in CIR -0.2% (95% CI; −9.1% to 8.8%).

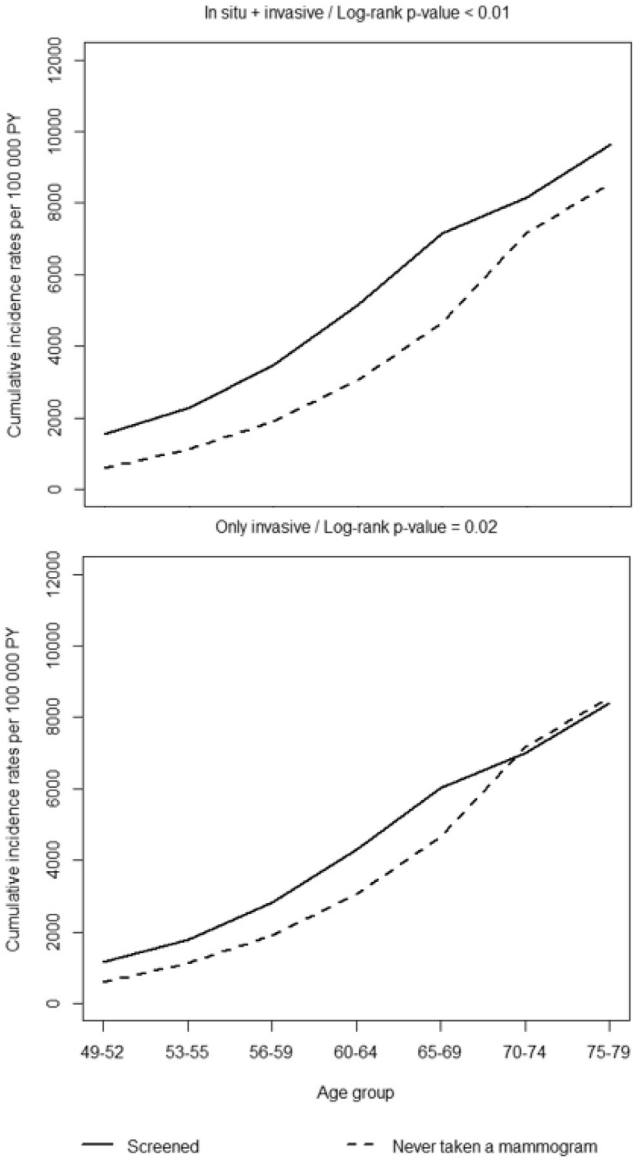

Fig. 4. Cumulative incidence rates of invasive breast cancer per 100 000 person-years for screened women and women who had never had a mammogram, *in situ* and invasive combined and invasive alone, the Norwegian Women and Cancer cohort, 2005–2013.

3.5. Breast cancer size and lymph node status

When looking at the cumulative incidence of invasive breast cancer stratified by tumour size and lymph node status (Fig. 5), screened women had smaller tumours (<2.5 cm) than unscreened women (p = 0.01). There was a borderline significant decrease in lymph node involvement among screened women (p = 0.06).

4. Discussion

In this analysis, women participating in the screening program had a higher incidence for invasive and *in situ* breast cancer combined compared with women who *never had a mammogram,* a difference which disappeared in the analysis restricted to invasive breast cancer only. It is the only European cohort study that can discriminate between women screened, unscreened and never taken a mammogram for proper comparisons of incidence rates.

The validity of the analyses is partly dependent on the prospective design of the NOWAC study. It is the only national cohort study in Europe with a random sample from the whole female population and with an acceptable response rate [13]. This has given distributions of major risk factors for breast cancer close to the expected population values [16]. The cumulative incidence rate curves for invasive breast cancer in the NOWAC cohort were not statistically significantly different from those published by the Cancer Registry of Norway. The slight increase in cumulative breast cancer incidence could be related to the increased proportion of women with

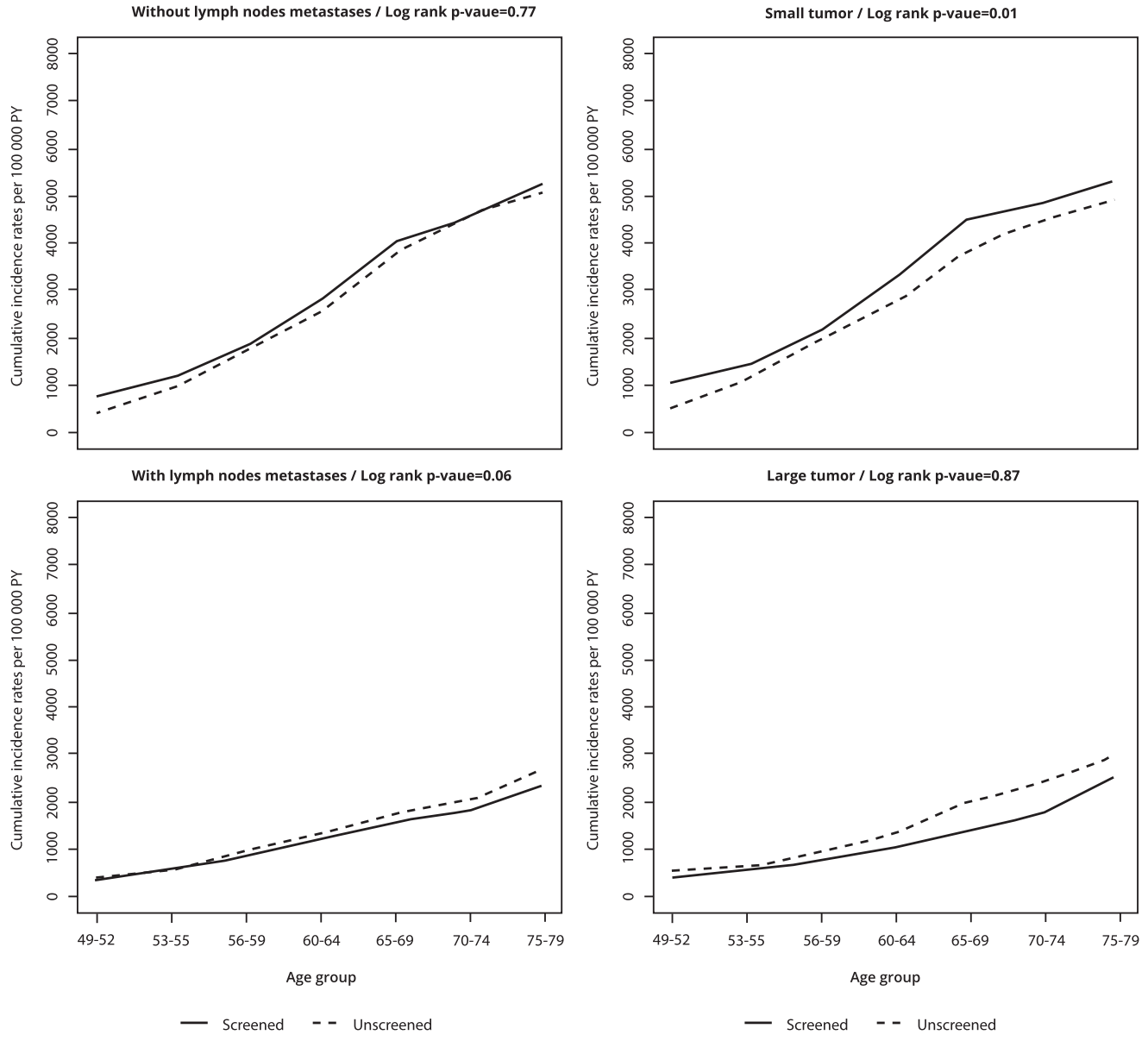

Fig. 5. Cumulative incidence rates of breast cancer according to screening status (only invasive), tumour size and lymph node involvement, the Norwegian Women and Cancer cohort, 2005–2013.

higher educations, who have been reported to have a slightly higher incidence rate. The information on mammograms in the screening program was based on a linkage to the NBCSP database using a unique personal identification number, the same as used for linkages to cancer registry and for mortality, resulting in complete coverages. For the first time, the non-screened, often named control group, could be divided into two sub-cohorts; women with a mammogram taken outside screening, often named wild screening or in a clinical situation, and those who never had a mammogram. The high level of wild screening in Norway before and during the years of introduction of NBCSP has been addressed [17]. The lack of *in situ* diagnosis in the group who never had taken a mammogram supports the validity of the questionnaire information since the *in situ* diagnoses depend on having taken a mammogram.

After the introduction of the NBCSP in four counties in 1996, at least six studies [18–23] of overdiagnosis in Norway have been published. As illustrated in Fig. 6, the estimates of overdiagnosis have been reduced over time with the last ones all under the estimate given by the Norwegian Research Council of between 15% and 25% [6]. In Norway, the decrease in estimates may be due to longer follow-up after the screening became national in 2005 and improved designs. A similar trend was found for the mammographic screening in the Netherlands with an estimate of 3.6% in 2006 [24]. In an overview of mammographic screening in Europe, the conclusion was that the most plausible estimates ranged from 1% to 10% covering the Netherlands, Italy, Spain, Norway, Sweden, Denmark and UK [25]. It should be noted that these results on overdiagnosis are quite similar to those of a recently published randomised controlled trial [26], which showed no differences in breast cancer incidence for *in situ* or invasive breast cancer. The UK Age trial recruited women aged 39–41 years in the 1990s with repeated screening up to 50 years, after which they were included in the ordinary national breast cancer screening program. According to the GRADE system [27], the change in methodology from ecological analyses, to record linkage studies and finally cohort analyses with both register information and questionnaire information from those outside the screening should improve the quality of evidence. The impact of study design and the methods of calculation have been used as an argument for the discrepancies on overdiagnosis estimates as found in Denmark [28]. For many countries, no specific estimates of overdiagnosis are published with France as an example [29].

Analyses and estimates of overdiagnosis are clearly dependent on the definitions of 'participation or not' in the screening program. In most studies, the definition of 'screened' is based on 'intention to screen' analyses, in which all women, or an estimated fraction in a certain geographic area, are considered to be the part of the screened group without any individual information. This 'intention to screen' approach can inform us about the public health implications of a screening program, but it does not inform individual women about the risk

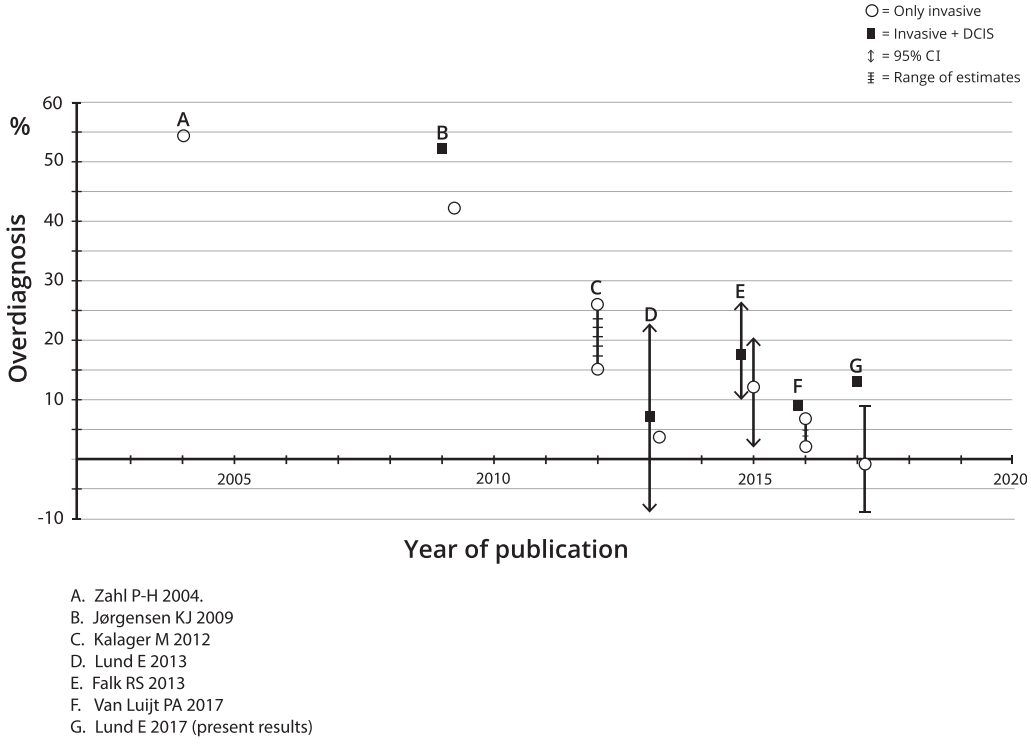

Fig. 6. Published estimates of overdiagnosis in the Norwegian Breast Cancer Screening Program [23–28] compared with the present analysis.

of overdiagnosis if they participate in screening. The present analysis took advantage of the unique opportunity to define the exact screening status of each participant after the complete implementation of a national breast cancer screening program, including the possibility to divide unscreened women into two subcohorts. The overall comparisons showed a tendency for more breast cancer in the unscreened group. However, since the unscreened group included many women with a maternal history of breast cancer, we considered it important to exclude this high-risk group in our analyses. Indeed, in Norway, women with a maternal history of breast cancer are offered genetic guidance and testing for genetic variants like BRC1, in addition to annual clinical breast examinations, mammography and eventually MRI. After we excluded women with a maternal history of breast cancer, we observed reduced cumulative incidence rates for both unscreened and screened women, though the effect was stronger for unscreened women. Another methodological issue was the definition of screen-detected cancer. Women who participated in the NOWAC study and were diagnosed with a breast cancer after screening interval period of more than 2 years were still counted as screened women. We did not have the information on the reasons why screened women stopped attending the NBCSP. It is possible that they were screened either in a different program, or were under specific surveillance, or decided to stop for personal reasons. This might overestimate the number of cases in the screened group. The cumulative incidence rate of breast cancer diagnosed more than 2 years after last mammogram was 0.4% for women under 70 years of age (data not shown). These cancers were diagnosed outside the screening program as clinical cancer.

Lead time is defined as the time between early diagnosis with screening and when diagnosis would have been made without screening. For Norway, lead time in the national screening program has been estimated till around five years [30]. Adjustment for lead-time bias can be done in several ways. We choose to follow the population 10 years after the end of the screening program till 79 years of age. We found a strong compensatory drop.

When discussing the issue of overdiagnosis in screening programs, it is important to mention the role of *in situ* tumours, mainly ductal carcinoma *in situ*. Screening presumes the existence of a silent disease reservoir [31]. The detection of these tumours is one of the primary goals of breast cancer screening, as they cannot be detected clinically. Although the level of progression from *in situ* to invasive breast cancer is unknown [12], the diagnosis and removal of *in situ* tumours should reduce progression to invasive cancer and result in a lower incidence of invasive breast cancer in older age groups. This was found in an ecological analysis of local screening units of the national screening program in England, Wales and Northern Ireland [32]. For every three screen-detected cases of ductal carcinoma *in situ*, there was one fewer invasive interval cancer in the next 3 years. Our results are compatible with such a weak tendency.

Another important result was the finding that the distribution of node-positive tumours and tumour size were more favourable among screened women compared with all unscreened women. These findings indicate that the screening works as planned by reducing the tumour burden of the screened population. The borderline significant reduction in node involvement could be important for the future mortality.

The NBCSP is a full-scale national program that uses digital mammography as a screening test. It has been shown that the number of unnecessary biopsies and other investigations declined after the nationwide introduction of digital mammography in Norway [33]. The percentage distribution of *in situ* and invasive breast cancers that we observed was quite similar in the screened and unscreened groups, supporting the view that most unscreened women do have taken mammograms, even if they are outside the NBCSP. One explanation for the small differences in the percentage distribution could be the strong time dependency of HRT use in Norway. Around the year 2000, the use of HRT increased rapidly, only to decline in subsequent years. At that time, public prescription rules advocated a mammogram before starting use of HRT. Also around the year 2000, the population-attributable risk of breast cancer related to current HRT use was estimated at 27% based on the NOWAC study [34]. HRT can affect the sensitivity of mammography, and changes in HRT use have been linked to increased risks of recall, biopsy rates, screen-detected cancers, and interval cancers [10]. The drop in HRT use could have improved the sensitivity of the NBCSP during the study period.

A weakness of the present study is the limited statistical power for the analyses of unscreened women, particularly for the very small group of women who never had a mammogram. Another problem could be the definition of women who never had a mammogram. This was based on questionnaire information given at the start of study period, and some of these women may have been screened outside NBCSP or taken a clinical mammogram thereafter. Women screened outside NBCSP would give a misclassification and add women with a mammogram to the group of women who never had a mammogram. We have no information on the number of women in this group. On the other hand, in this analysis women who never had a mammogram had no *in situ* breast cancer indicating that they have not had any wild-screening investigations.

This analysis complements a previous analysis of overdiagnosis in the NOWAC study based on questionnaire information only [21]. The present analysis added register information from the NBCSP giving

exact information on screening status, a larger study population and longer follow-up.

Statistical estimations will hardly be able to solve the problem of potential overdiagnosis, but they have played an important role in pinpointing the need for improved radiological and histopathological diagnostics that can give differential diagnoses for growing and non-growing tumours. The implication of the concept of overdiagnosis is a postulate that current histopathological diagnostic is not sensitive enough for the differential diagnosis of overdiagnostic cases versus cases in need of treatment. Consequently, the diagnosis of non-growing or overdiagnosed tumours might be solved through new independent tests [35,36] for breast cancer that are based on tumour tissue or peripheral blood using functional genomics.

5. Conclusion

Our analysis did not find evidence for overdiagnosis of invasive breast cancer in the NBCSP. Screened women had smaller tumours and less lymph node involvement. The early detection of *in situ* tumours is a primary goal of screening and should not be considered overdiagnosis. The discussion of the negative health effects of screening should focus on the potential problem of overtreatment of *in situ* tumours.

Ethics approval and consent to participate

Each NOWAC participant has a unique study number which can be linked to their national identifier by Statistics Norway but is kept anonymous to researchers. Participating women gave informed consent at the start of follow-up. The NOWAC study was approved by the Norwegian Data Inspectorate and by the Regional Medical Ethical Committee of North Norway (REK). Linkages of the NOWAC study to the national Cancer Registry of Norway, registries on death and emigration were approved by the Directorate of Health.

Consent for publication

Not necessary.

Availability of data and material

The data sets generated during and/or analysed during the current study are not publicly available due to Norwegian laws handling medical research data but are available from the corresponding author on reasonable request.

Conflict of interest statement

None declared.

Funding

This study was supported by a grant from the Norwegian Research Council: grant 189505. The funders had no role in the design of the study; in the collection, analyses and interpretation of the data; in the writing of the manuscript; or in the decision to submit for publication.

Authors' contributions

EL was the PI of the study and participated in design, analyses and drafted the manuscript. AN did the statistical analyses and revised the manuscript. J-CT participated in the statistical analyses and revised the manuscript.

Acknowledgements

The authors are thankful to the women who participated in this cancer research project. Bente Augdal, Merete Albertsen and Knut Hansen were responsible for all infrastructure and administrative issues.

References

[1] Biller-Andorno N, Juni P. Abolishing mammography screening programs? A view from the Swiss Medical Board. NEJM 2014; 370:1965–7.
[2] Marmot MG, Altman DG, Cameron DA, Thompson SG, Wilcox M. Independent UKPBCS: the benefits and harms of breast cancer screening: an independent review. Lancet 2012;380: 1778–86.
[3] Goetzsche PC, Joergensen KJ. Screening for breast cancer with mammography. The Cochrane Library. John Wiley & Sons; 2013. Issue 6.
[4] Paci E, Broeders M, Hofvind S, Puliti D, Duffy SW, EUROSCREEN Working Group. European breast cancer service screening outcomes: a first balance sheet of the benefits and harms. CEBP 2014;23:1159–63.
[5] Lauby-Secretan B, Scoccianti C, Loomis D, Straif K. Breast cancer screening – viewpoint of the IARC Working Group. N Engl J Med 2015;372:2353–8.
[6] The Research Council of Norway. www.forskningsradet.no/publikasjoner Research-based evaluation of the Norwegian Breast Cancer Screening Program. Final report.
[7] Harding C, Pompei F, Burmistrov D, Welch HG, Abebe R, Wilson R. Breast cancer screening, incidence, and mortality across US counties. JAMA Intern Med 2015;175(9):1483–9. https://doi.org/10.1001/jamainternmed.2015.3043.
[8] Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, et al. Benefits and harms of breast cancer screening: a systematic review. JAMA 2015;314(15):1615–34. https://doi.org/10.1001/jama.2015.13183.
[9] Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of breast cancer screening: systematic review to update the 2009 U.S. Preventive services task force recommendation. Ann Intern Med 2016 Feb 16;164(4):256–67. https://doi.org/10.7326/M15-0970 [Epub 2016 Jan 12].
[10] Njor SH, Hallas J, Schwartz W, Lynge E, Pedersen AT. Type of hormone therapy and risk of misclassification at mammography

screening. Menopause 2011;18(2):171–7. https://doi.org/10.1097/gme.0b013e3181ea1fd5.
[11] Moller P, Stormorken A, Jonsrud C, Holmen MM, Hagen AI, Clark N, et al. Survival of patients with BRCA1-associated breast cancer diagnosed in an MRI-based surveillance program. Breast Cancer Res 2013;139:155–61.
[12] Cowell CF, Weigelt B, Sakr RA, Ng CK, Hicks J, King TA, et al. Progression from ductal carcinoma in situ to invasive breast cancer: revisited. Mol Oncol 2013;7:859–69. https://doi.org/10.1016/j.molonc.2013.07.005.
[13] Lund E, Dumeaux V, Braaten T, Hjartåker A, Engeset D, Skeie G, et al. Cohort profile: the Norwegian women and cancer study – NOWAC – Kvinner og kreft. Int J Epidemiol 2008;37(1):36–41.
[14] Cancer Registry of Norway. Cancer in Norway 2011-Cancer incidence, mortality, survival and prevalence in Norway. Oslo: Cancer Registry of Norway; 2013.
[15] Jensen OM, Parkin DM, MacLennan R, Muir CS, Skeet RG. Cancer registration: principles and methods. IARC Scientific Publication; 1991. No. 95 [chapter 11].
[16] Lund E, Kumle M, Braaten T, Hjartåker A, Bakken K, Eggen E, et al. External validity in a population-based national prospective study – the Norwegian Women and Cancer Study (NOWAC). Cancer Causes Control 2003;10:1001–8.
[17] Lynge E, Braaten T, Njor SH, Olsen AH, Kumle M, Waaseth M, et al. Mammography activity in Norway 1983 to 2008. Acta Oncol 2011;50:1062–7.
[18] Zahl P-H, Heine-Strand B, Mæhlen J. Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study. BMJ 2004:921–4.
[19] Jørgensen KJ, Gøtzsche PC. Overdiagnosis in publicly organized mammography screening programmes: systematic review of incidence trends. BMJ 2009;339.
[20] Kalager M, Adami H-O, Bretthauer M, Tamini RM. Overdiagnosis of invasive breast cancer due to mammography screening: results from the Norwegian Screening program. Ann Int Med 2012;156:491–9.
[21] Lund E, Mode N, Waaseth M, Thalabard J-C. Overdiagnosis of breast cancer in the Norwegian breast Cancer Screening Program estimated by the Norwegian Women and Cancer cohort study. BMC Cancer 2013;13:614–22.
[22] Falk RS, Hofvind S, Skaane P, Haldorsen T. Overdiagnosis among women attending a population-based mammography screening program. Int J Cancer 2013;133:705–13.
[23] Van Luijt PA, Heijnsdiik EAM, van Ravesreyn NT, Hofvind S, de Koning HJ. Breast cancer incidence trends in Norway and estimates of overdiagnosis. J Med Screen 2017;24:83–91.
[24] De Gelder R, Heijnsdijk EAM, van Ravesteyn NT, Fracheboud J, Draisma G, de Konig HJ. Interpreting overdiagnosis estimates in population-based mammography screening. Epi Rev 2011;33:111–21.
[25] Pulit D, Duffy SW, Miccinesi G, de Konig H, Lynge E, Zappa M, Paci E and the Euroscreen Working Group. Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. J Med Screen 2012;19(Suppl. 1):42–56.
[26] Moss SM, Wale C, Smith R, Evans A, Cuckle H, Duffy SW. Effect of mammographic screening from age 40 years on breast cancer mortality in the UK Age trial at 17 years' follow-up: a randomised controlled trial. Lancet Oncol 2015 Sep;16(9):1123–32.
[27] http://www.gradeworkinggroup.org/.
[28] Lynge E, Beau A-B, Christiansen P, von Euler-Chelpin M, Kroman N, Njor S, et al. Overdiagnosis in breast cancer screening: the impact of study design and calculations. Eur J Cancer 2017;80:26–9.
[29] Editorial. Numero thematique – depistage organize du cancer de sein. BEH; 2012. 35-36-37: 389-90.
[30] Weedon-Fekjær H, Lindqvist BH, Vatten LJ, Aalen OO, Tretli S. Estimating mean sojourn time and screening sensitivity using questionnaire data on time since previous screening. J Med Screen 2008;15:83–90. https://doi.org/10.1258/jms.2008.007071.
[31] Welch G, Black W. Overdiagnosis in cancer. J Natl Cancer Inst 2010;102(9):605–13. https://doi.org/10.1093/jnci/djq099.
[32] Duffy SW, Dibden A, Michalopoules D, Offman J, Parmar D, Jenkins J, et al. Screen detection of ductal carcinoma in situ and subsequent incidence of invasive interval breast cancers: a retrospective population-based study. Lancet Oncol 2016;17:109–14.
[33] Hofvind S, Skaane P, Elmore JG, Sebuødegård S, Hoff SR, Lee CI. Mammographic performance in a population-based screening program: before, during, and after the transition from screen-film to full-field digital mammography. Radiology 2014;272(1):52–62.
[34] Bakken K, Alsaker E, Eggen AE, Lund E. Hormone replacement therapy and incidence of hormone-dependent cancers in the Norwegian Women and Cancer study. Int J Cancer 2004;112:130–4.
[35] Drukker CA, Schmidt MK, Rutgers EJT, Cardoso F, Kerlikowske K, Esserman LJ, et al. Mammographic screening detects low-risk tumor biology breast cancers. Breast Cancer Res Treat 2014;144:103–11.
[36] Dumeaux V, Ursini-Siegel J, Flatberg A, Fjosne HE, Frantzen JO, Holmen MM, et al. Peripheral blood cells inform on the presence of breast cancer: a population-based case-control study. Int J Cancer 2015;136:656–67. https://doi.org/10.1002/ijc.29030.