

Breast Cancer Screening Program in Lithuania: Interval Cancers and Program Sensitivity After 7 Years of Mammography Screening

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Abstract

Objective: Analysis of interval cancers is critical in determining the sensitivity of screening and represents an objective measure of the quality of mammography screening program (MSP).

Methods: Period analyzed: from 2006 to 2012. The rate of screen-detected, interval cancers and program sensitivity were measured. A comparison of screen-detected and interval cancers was performed.

Results: During the period of the study, 429 473 women were screened and 1297 were found to have cancer. The overall screen-detected cancer rate was 30.2 per 10 000 women screened. Four hundred thirty-one case of interval cancers have occurred during the period of the study. The interval cancer ratio (ICR) was 0.25. Overall sensitivity of MSP amounted to 75.1%. Slightly lower sensitivity was found among the youngest age-group, especially for those with lobular cancers. Interval cancers were bigger in size, more often with metastases in lymph nodes, than screen-detected cancers, but these differences were not statistically significant.

Conclusions: Overall program sensitivity in Lithuania is about 75%, ICR is 0.25, and these parameters are comparable to other European countries.

Keywords

breast cancer, screening program, interval cancers, program sensitivity

Received February 8, 2019. Received revised June 23, 2019. Accepted for publication July 31, 2019.

Introduction

Since the introduction of screening, breast cancer is described as screen-detected cancer, interval cancer, or symptomatic cancer. Interval cancers, according to the National Health Service Breast Screening Programme definition and European guidelines, are breast cancers diagnosed in the interval between the scheduled screening episodes in women screened and given a “normal” screening result—that is, the previous screening was negative.^{1,2} An interval cancer can be detected “de novo” due to the rapid tumor growth or a failure in the screening process. Interval cancers are inevitable in any screening program, but their

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number should be kept as low as possible, in order not to decrease the effectiveness of the program.³

Analysis of interval cancers is critical in determining the sensitivity of screening and represents an objective measure of the quality of the screening program, implicating that increased detection of cancers in the program must lead to a lower incidence of interval cancers.⁴ Therefore, the detection rate of interval cancers is a key component of quality control for the screening programs. The comprehensive multidisciplinary guidelines for quality assurance in (breast?) cancer screening have been developed.^{1,5} These guidelines include the monitoring of organizational, technical, and professional performances, as well as the evaluation of an impact, as an integrative parts of cancer screening programs. The European guidelines for breast cancer screening and diagnosis strongly recommend epidemiological and radiological monitoring of interval cancers. Monitoring of interval cancer occurrence is a crucial part of the mammography screening program (MSP) because it provides a way of evaluation for some of the technical processes involved in the screening (eg, carrying out and the interpretation of mammograms). It also contributes to the evaluation of the impact of mammography screening on breast cancer in the target population.⁶ Interval cancers allow assessing the sensitivity of the entire screening program, that is, estimating the overall impact of the screening program in detecting cancers in the screened population.¹

In 2005, the MSP was started in Lithuania. In a recent report on cancer screening in the European Union (EU), Lithuania was the country with the lowest participation rate (44.9% in 2014) and one of 3 countries where a centrally organized invitation through a screening registry is not implemented.⁷ The aim of this study was to evaluate the rate of the interval cancers and program sensitivity for the first time in our country and to compare the main characteristics of screen-detected and interval cancers.

Materials and Methods

Breast Cancer Screening Program in Lithuania

The breast cancer screening program in Lithuania was started in 2005, after the order of the Lithuanian Health Care Ministry was published, regarding the funding program for the screening of breast cancer. According to the program, the target population is defined as women aged 50 to 69 years. There is no centrally organized invitation system established in Lithuania. Women are referred to a screening mammography by their general practitioners. Mammography is performed every 2 years. Craniocaudal and mediolateral oblique mammograms are obtained and read independently by 2 radiologists. Both screen-film, computed and digital mammography systems are used. For the reporting of screening and additional imaging results, the *Breast Imaging Reporting and Data System* (BIR-ADS) system is used, and for the evaluation of breast density, typology according to the *American College of Radiology* (ACR) is included.⁸ Information from the assessment is sent

within 2 weeks to the general practitioner. At the beginning, there were 18 units in the screening program, and by the year 2017, 31 screening units are taking part in the program. Some of them only perform mammograms, while others are performing and evaluating the results of the screening. Only 5 of those centers are specialized for additional examinations, such as ultrasound, magnetic resonance imaging, stereotaxic biopsy, and core needle biopsy. These centers also provide specific treatment, in case breast cancer is detected during the screening. There is no recall system established if suspicious findings are detected during the screening. In daily practice, general practitioner provides the information about the results of the screening mammogram and, in case of suspicious changes, refers the patient to an oncologist for further investigation.

Data Sources

Analysis was based on data acquired from the population-based Cancer Registry and from National Health Insurance Fund (NHIF).

The Lithuanian Cancer Registry is a population-based cancer registry that contains personal and demographic information (place of residence, sex, date of birth, and vital status), as well as the information on the diagnosis (cancer site, histology, date of diagnosis, and method of cancer verification) and death (date of death and cause of death) of all patients with cancer in Lithuania. The main sources of information on cancer cases are primary, secondary, and tertiary health-care institutions in the country, which are responsible for notifying the registry when cancer is diagnosed. All physicians, all hospitals, and other institutions in the country must send a notification to the Lithuanian Cancer Registry of all the cancer cases that come to their attention. The notifications, which are supplemented by the information from a death certificate, are built into the database, which can be used for statistical analysis. This database contains information on all cancer cases diagnosed in Lithuania since 1978. Since the period 1988 to 1992, the Registry data have been included in the "Cancer Incidence in Five Continents."⁹

Data regarding the participation rate in Lithuanian MSP were acquired from Lithuanian NHIF. The NHIF database is used for the management, storage, exchange, analysis, and reporting of all the services provided by the health-care institutions. This database also contains information about all the performed mammograms and their results.

The linkage between these 2 systems was created in order to evaluate breast cancers detected during MSP and interval cancers and in order to compare general characteristics of screen-detected and interval cancers.

Methods

The study encompasses period from 2006 (when MSP was fully implemented in Lithuania) to 2012 (reliable data from Cancer registry about the incidence of cancer). Invasive

cancers, which were proven histologically after BIRADS 4, BIRADS 5, and BIRADS 0 assessment categories, were chosen as screen-detected cancers. Only invasive breast cancer was included because the Registry is not collecting data on *carcinoma in situ*. Interval cancers were defined as primary invasive breast cancers, which were diagnosed in women who had a screening test, which was negative for malignancy (BIRADS 1, BIRADS 2, BIRADS 3) and the cancer was diagnosed in 90 to 730 days after the screening test.

The following outcome measures were calculated: the rate of screen-detected cancers, the rate of interval cancers, and program sensitivity. A comparison of the major characteristics between screen-detected and interval cancers was also performed.

The rate of screen-detected cancers was calculated using the following formula:

$$\begin{aligned} &\text{Rate of screen – Detected cancers} \\ &= \frac{\text{Number of screen – Detected cancers}}{\text{Number of women screened}} \times 10,000. \end{aligned}$$

The rate of interval cancers was calculated likewise.

Interval cancer ratio (ICR) was calculated using the following formula¹⁰:

$$\text{ICR} = \frac{\text{Interval cancers}}{\text{Interval cancers} + \text{Screen – Detected cancers}}.$$

The overall sensitivity of the screening program was assessed as recommended in the European guidelines¹ using the following formula:

$$\begin{aligned} &\text{Program sensitivity} \\ &= \frac{\text{Screen – Detected cancers}}{\text{Interval cancers} + \text{Screen – Detected cancers}}. \end{aligned}$$

The program sensitivity for invasive breast cancer was further determined with a respect to age-groups and histological subtypes. The age was calculated at the time of the diagnosis.

In order to compare the main characteristics of screen-detected cancers and interval cancers, 2 groups of women were chosen: women with breast cancer detected during MSP and women with breast cancer detected after screening test which was negative for malignancy in the period equal to one screening round (730 days).

Program sensitivity is reported as a percentage with 95% confidence intervals (CIs). The 95% CIs were calculated assuming a Poisson distribution. Differences among subgroups were tested using chi-square test. Mann-Whitney *U* test was used to see if the difference in mean age at the diagnosis had a significant difference.

Results

Every year about 1,500 new invasive breast cancer cases are being diagnosed in Lithuania. However, cancers detected through MSP account for only a small fraction of all the cancer cases diagnosed among women of 50 to 69 years of age (Table 1). During the study period, 1297 cancers were detected

through MSP and 431 interval cancers. Rates of interval cancers are presented in Table 2.

The overall screen-detected breast cancer rate was 30.2 per 10,000 women screened (1297/429,473). Proportion of cancers detected during screening is increasing; however, they account for only about one quarter of all the cancers diagnosed in women aged 50 to 69 years. The ICR ranged from 0.23 to 0.33. The overall ICR was 0.25 (431/431 + 1297).

When comparing the main characteristics of cancers detected during screening and interval breast cancers, it was found that interval cancers were bigger in size, more often had lymph node metastases, and more often had lobular histology than screen-detected cancers; however, these differences were not statistically significant (Table 3).

During the study period among women, who had negative results from screening, 431 cases of interval breast cancers have occurred. Overall sensitivity of Lithuanian MSP amounted to 75.1% (95% CI: 71.1%-79.3%). Program sensitivity according to age and histological subtype is shown in Table 4. Age-group and histological subtype had an influence on the sensitivity of the program. Slightly lower sensitivity was found among the youngest age-group (69.0%; 95% CI: 54.5%-87.4%), especially for those with lobular cancer subtype (60.0%; 95% CI: 19.4%-186.0%).

Discussion

During this study, we have found that only 25% of cancers in women aged 50 to 69 years were diagnosed during MSP. The ICR ranged from 0.23 to 0.33 and the overall ICR was 0.25. Overall sensitivity of Lithuanian MSP amounted to 75.1%. Interval cancers were bigger in size, more often had lymph node metastases, and more often had lobular histology than screen-detected cancers; however, these differences were not statistically significant.

Since interval cancers represent the sensitivity of breast cancer screening programs and they are considered as an adverse outcome for women participating in the programs, surveillance of interval breast cancers is routinely practiced and strongly recommended by EU guidelines.^{1,11} Estimation of the incidence of interval cancers in screening programs requires a standardized method for identification, collection, and assessment of the cases. A considerable number of reviews of the incidence of interval cancers in randomized controlled trials and population-based screening programs have been performed,¹²⁻¹⁶ as well as reviews on pooled data at regional, national, and international levels.¹⁷⁻²² One study was focused on epidemiological surveillance (interval cancers rates), while others highlighted the radiological review of tumors or the differences in the biology and prognosis of interval cancers compared to screen-detected cancers.

It was highlighted by several investigators that various methodological and analytic parameters can substantially influence the estimation of interval breast cancers rates and other epidemiologic measures of interval cancers.²³⁻²⁵ These include variability in the definition of interval breast cancers;

Table 1. Breast Cancer in Women (Total, Screen Detected) in Lithuania in 2006-2012.

Years	Breast Cancer (Total)	Number of Women Aged 0-69 Years of Age	Breast Cancer (50-69 years)	Number of Women Screened	Screen-Detected Cancers	Screen-Detected Cancer Rate/10,000 Screened	Proportion From All Cancers in 50-69 years group
2006	1436	407 215	765	48 540	114	23.49	14.9
2007	1378	404 849	653	47 396	195	41.14	29.9
2008	1534	404 328	742	52 670	187	35.50	25.2
2009	1527	406 129	733	59 150	190	32.12	25.9
2010	1490	409 336	735	61 537	180	29.25	24.5
2011	1544	411 029	798	76 902	206	26.79	25.8
2012	1531	413 596	784	83 278	225	27.02	28.7
Total	10 440	408 068	5210	429 473	1297	30.20	24.89

Table 2. Interval Breast Cancers in Lithuania in 2006-2012.

Years	Interval Cancers	Interval Cancer Rate/10,000 Screened	Interval Cancer Ratio (ICR)
2006	40	8.24	0.26
2007	64	13.50	0.25
2008	74	14.05	0.28
2009	84	14.20	0.31
2010	89	14.46	0.33
2011	62	8.06	0.23
2012	18 ^a	2.16 ^a	0.07 ^a

^aBased on 1-year observation.

false-negative assessment case inclusion/exclusion; the adequacy of ascertainment of interval cancers, adequacy of cancer notification and registration; participation rate; age range; interval length; recall rate; and underlying breast cancer rates or burden on the population. Early detection outside of the program may influence the interval cancers by detecting asymptomatic cases that would, otherwise, be diagnosed in the following screen.²⁶ Two-view mammography and independent double reading would also result in lower interval cancer rates as compared with one-view and single reading.²⁶ Recall rate reflects the radiological workup and a high recall rate may result in a lower interval cancer rate.²⁷ International comparisons of interval cancers are important but should be made cautiously due to the lack of standardized surveillance methods.²⁵

Our study shows that only about one quarter of breast cancers in women aged 50 to 69 years are diagnosed during MSP. It reflects the low participation rate. The main reason for it can be the lack of centrally organized invitation system in Lithuania. Women acquiring the information about program only from general practitioners can also contribute to the level of participation rate.

Usually, the number of screen-detected cancers is higher in initial screens than in subsequent ones^{10,28}; however, it was not the case in our program. The number of screen-detected cancers was lower in the first screening years than in later ones. The reason for this can be the low participation rate during the first years (14% in 2006 and 20.5% in 2012). The fact that the

number of screen-detected cases is higher in initial screens than in subsequent ones leads to the ICR being lower in initial screens versus subsequent screens. The ICR was 0.26 in the first year of screening and increased to 0.33 in the 2010. The decrease in the last year can be due to the fact that women screened in 2012 had follow-ups for interval cancers only for 1 year. Interval cancer rate per 10 000 women screened increased from 8.24 in the first year of screening to 14.46 in 2010. It should be mentioned that in our study ICR might be underestimated, due to interval cancer definition used.

Andersen with colleagues¹⁰ conducted a systematic review of 12 screening programs in Europe and counted ICR for initial and subsequent screening rounds. The ICR varied from 0.10 to 0.28 covering initial screens only. For subsequent screens, the ICR varied from 0.22 to 0.37, with the highest and the lowest ratios in the same programs. Study of 6 European countries showed the interval cancer rates ranging from 0.8 to 2.1 per 1000 women screened in the 24 months period following screening, for women aged 50 to 69 years.²⁶ A collaborative study in 4 European centers, Coimbra (Portugal), Dublin (Ireland), Stockholm (Sweden), and Turin (Italy), counted IC rates for each centre: 4.3/10 000 in Coimbra, 23.8/10 000 in Dublin, 18/10 000 in Stockholm, and 16.7/10 000 in Turin.⁶ Researches from this study highlighted that they have found differences between the centers in organizational aspects, way of invitation, ability to cover the entire target population, methods of ascertainment of breast cancer, background incidence of breast cancer in the target population, and in the IC rates themselves of the screening programs. Each aspect has a potential to impact the interpretation of the data of all the interval cancers and can interfere with the validity of comparisons of data between the centers.

We were not able to evaluate some of the performance indicators, such as technical repetition rate, additional imaging rate at the time of screening, recall rate, and benign to malignant biopsy ratio. These indicators can influence the rate of interval cancers. The main information collected by NHIF is information provided to the women about MSP, mammograms performed, and evaluation of mammograms.

Diagnosis of interval breast cancers is associated with several factors, which include younger age, premenopausal status,

Table 3. Differences Between Screen-Detected and Interval Breast Cancers.

Characteristics	Screen-Detected Cancers (n = 1297)		Interval Cancers (n = 431)		P Value
	Cases	%	Cases	%	
Mean age at diagnosis, years (SD)	61.8 (4.5)		61.9 (4.7)		
Histological type					.06
Ductal	969	74.7	300	69.6	
Lobular	123	9.5	54	12.5	
Other	161	12.4	65	15.1	
Unknown ^a	44	3.4	12	2.8	
Tumor size					.26
T1	823	63.5	257	59.6	
T2	350	27.0	132	30.6	
T3	24	1.9	11	2.6	
T4	35	2.7	8	1.9	
Unknown ^a	6	5.0	23	5.3	
Nodal status					.23
Positive	432	33.3	157	36.4	
Negative	747	57.6	235	54.5	
Unknown ^a	118	9.1	39	9.0	
Metastasis					.38
Positive	31	2.4	14	3.2	
Negative	1083	83.5	368	85.4	
Unknown ^a	183	14.1	49	11.4	
Stage					.16
I	632	48.7	191	44.3	
II	441	34.0	142	32.9	
III	163	12.6	67	15.5	
IV	35	2.7	17	3.9	
Unknown ^a	26	2.0	14	3.2	

^aUnknown category was not included calculating the tests for difference.

lower body mass index, use of hormone therapy, and greater mammographic density.^{29,30}

Reports on the association between interval cancers and histological subtype of breast cancer are sparse and investigated mainly in the subsequent screening episodes. Data from screening programs in Vermont, Norway, and the Netherlands all indicate substantially lower program sensitivity for lobular than for nonlobular breast cancers.³¹⁻³³ Data from Ontario Breast Cancer Screening Program³⁴ indicate that real interval cancers were almost twice as likely to have nonductal, that is, mainly lobular morphology, suggesting also a lower program sensitivity in lobular disease.

In our study, we showed that the highest program sensitivity (75.8%) was in oldest participant group (age 65-69 years) and for those with ductal histology (77.0%). Data are very similar to a German study,³¹ which has reported that sensitivity of the program increased with age and was the greatest in nonlobular breast cancers and in DCIS. Among young participants with invasive breast cancer, particularly those with a lobular subtype, program sensitivity was markedly decreased.

Overall program sensitivity in Lithuania is comparable to other countries where the average sensitivity is about 75%. The

Table 4. Program Sensitivity by Age and Tumor Type.

Characteristics	Screen-Detected Cancers		Interval Cancers		Program Sensitivity % [95% Confidence Interval]
	Cases	%	Cases	%	
Age					
50-54	69	5.3	31	7.2	69.0 [54.5-87.4]
55-59	368	28.4	121	28.1	75.3 [67.9-83.4]
60-64	442	34.1	140	32.5	75.9 [69.2-83.4]
65-69	405	31.2	129	29.9	75.8 [68.8-83.6]
Total	1297	100.0	431	100.0	75.1 [71.1-79.3]
Histology					
Lobular	123		54		69.5 [58.2-82.9]
Ductal	969		300		76.4 [71.7-81.3]

sensitivity of MSP has a wide range of reported values. In a review of 13 reports from the literature from 1990 to 1999, the range for sensitivity was 68% to 92%.³⁵ In Germany, a reported MSP sensitivity on average was 78.2%, and increased from 72.1% at age of 50 to 54 years to 82.4% at age of 65 to 69 years ($P < .0001$).³¹ In a pooled analysis of European MSP data from 6 countries, the average program sensitivity was 72%.²⁶ In this analysis of interval cancers rates in 6 European countries, Tornberg with colleagues have evaluated interval cancers rates and program sensitivity. They used common data collection protocol to explore the differences in interval cancers rates among the programs. Pooled analysis was used to describe interval cancers rates by age, compliance in screening, recall rate, screening detection rate, and expected breast cancer incidence. The total sensitivity for all 8 MSPs from 6 European countries included was 72%, the highest sensitivity (84%) being for Torino (Italy) MSP and the lowest (67%) for Strasbourg (France) MSP.

Some published studies showed that interval and screen-detected cancers have different clinic-pathological characteristics. Interval breast cancers in some studies are found to be larger, to have more advanced stage, and express proliferative markers more often than screen-detected cancers.³⁶⁻³⁸ Interval cancers tend to have worse prognosis, with a higher proportion of large tumors, lymph node involvement, advanced stages, high histologic grade, and negative hormone receptors.^{34,39,40}

In our study, we did not find significant differences between screen-detected and interval cancers. There is a number of studies, performing radiological surveillance of interval cancers, trying to classify them into categories and looking for the incidence rates, reasons for the occurrence of each category, and differences in their biology and prognosis.¹¹ In our study, we were unable to perform such analysis due to the lack of screening registry, since the mammographic images are not stored in one PACS or other archive and there is no possibility to review the screening mammograms. The abovementioned problems with program implementation in Lithuania may have led to the fact that no difference between screen-detected cancers and interval cancers was found.

Conclusions

This study provides an important evaluation of Lithuanian MSP. Number of interval cancers and program sensitivity is assessed for the first time since the program in Lithuania has been started. These parameters are essential for the evaluation of MSP in every country. Overall program sensitivity in Lithuania is about 75%, ICR is 0.25, and these parameters are comparable to other European countries.

Authors' Note

Ethics approval and consent of participants was not necessary, as this study involved the use of a de-identified database according to Lithuanian and National Cancer Institute legislation.




Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

- Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L, eds. *European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis*. Luxembourg, Europe: Office for Official Publications of the European Communities; 2006.
- NHS Breast Screening Radiologists Quality Assurance Committee. *Quality Assurance Guidelines for Breast Cancer Screening Radiology*. Sheffield, England: NHSBSP Publications; 2005.
- Bordas P, Jonsson H, Nystrom L, Lenner P. Interval cancer incidence and episode sensitivity in the Norrbotten Mammography Screening Programme, Sweden. *J Med Screen*. 2009;16(1):39-45.
- Renart-Vicens G, Puig-Vives M, Albanell J, et al. Evaluation of the interval cancer rate and its determinants on the Girona health region's early breast cancer detection program. *BMC Cancer*. 2014;14:558.
- Perry N, Broeders M, de Wolf C, Tornberg S, Holland R, von Karsa L, eds. *European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis*. 4th ed. Supplements. Luxembourg, Europe: European Commission, Publications Office of the European Union; 2013.
- Tornberg S, Codd M, Rodrigues V, Segnan N, Ponti A. Ascertainment and evaluation of interval cancers in population-based mammography screening programmes: a collaborative study in four European centres. *J Med Screen*. 2005;12(1):43-49.
- Cancer Screening in the EU. 2nd Report on the Implementation of the Council Recommendation. 2017; https://ec.europa.eu/health/major_chronic_diseases/publications_en. Accessed April 23, 2017.
- American College of Radiology. *Illustrated Breast Imaging Reporting and Data System*. Reston, VA: American College of Radiology; 1998.
- Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. *Cancer Incidence in Five Continents*. Vol. VIII. Lyon, France: International Agency for Research on Cancer; 2002.
- Andersen SB, Tornberg S, Lynge E, Euler-Chelpin M, Njor SH. A simple way to measure the burden of interval cancers in breast cancer screening. *BMC Cancer*. 2014;14:782.
- Houssami N, Hunter K. The epidemiology, radiology and biological characteristics of interval breast cancers in population mammography screening. *NPJ Breast Cancer*. 2017;3:12.
- Bjurstam N, Björnelid L, Duffy SW, et al. The Gothenburg breast screening trial. First results on mortality, incidence and mode of detection for women 39–49 years at randomization. *Cancer*. 1997;80(11):2091-2099.
- Frisell J, Eklund G, Hellstrom L, Somell A. Analysis of interval carcinoma in a randomised screening trial in Stockholm. *Breast Cancer Res Treat*. 1987;9(3):219-225.
- Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoft O. Update of the Swedish two-county program of mammographic screening for breast cancer. *Rad Clin N Am*. 1992;30(1):187-210.
- Vitak B. Invasive interval cancers in the Ostergotland Mammographic Screening Programme: radiological analysis. *Eur Radiol*. 1998;8(4):639-646.
- Zackrisson S, Janzon L, Manjer J, Andersson I. Improved survival rate for women with interval breast cancer—results from the breast cancer screening programme in Malmo, Sweden. *J Med Screen*. 2007;14(3):138-143.
- Day N, McCann J, Camilleri-Ferrante C, et al. Monitoring interval cancers in breast screening programmes: the east Anglian experience. *J Med Screen*. 1995;2(4):180-185.
- Fracheboud J, de Koning HJ, Beemsterboer PMM, et al. Interval cancers in the Dutch breast screening programme. *Br J Cancer*. 1999;81(5):912-917.
- Kavanagh AM, Mitchell H, Farrugia H, Giles GG. Monitoring interval cancers in an Australian mammographic screening programme. *J Med Screening*. 1999;6(3):139-143.
- Peeters PH, Verbeek AL, Hendriks JH, Holland R, Mravunac M, Vooijs GP. The occurrence of interval cancers in the Nijmegen screening programme. *Br J Cancer*. 1989;59(6):929-932.
- Wang H, Bjurstam N, Bjorndal H, et al. Interval cancers in the Norwegian breast cancer screening program: frequency, characteristics and use of HRT. *Int J Cancer*. 2001;94(4):594-598.
- Zappa M, Falini P, Bonardi R, et al. Monitoring interval cancers in mammographic screening: the Florence District Programme Experience. *Breast*. 2002;11(4):301-305.
- Bulliard JL, Sasieni P, Klabunde C, De Landtsheer JP, Yankaskas BC, Fracheboud J. Methodological issues in international comparison of interval breast cancers. *Int J Cancer*. 2006;119(5):1158-1163.
- Hofvind S, Yankaskas BC, Bulliard JL, Klabunde CN, Fracheboud J. Comparing interval breast cancer rates in Norway and

- North Carolina: results and challenges. *J Med Screen*. 2009;16(3):131-139.
25. Houssami N, Irwig L, Ciatto S. Radiological surveillance of interval breast cancers in screening programmes. *Lancet Oncol*. 2006;7(3):259-265.
 26. Tornberg S, Kemetli L, Ascunce N, et al. A pooled analysis of interval cancer rates in six European countries. *Eur J Cancer Prev*. 2010;19(2):87-93.
 27. Otten JD, Karssemeijer N, Hendriks JH, et al. Effect of recall rate on earlier screen detection of breast cancers based on the Dutch performance indicators. *J Natl Cancer Inst*. 2005;97(10):748-754.
 28. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA*. 2009;302(15):1685-1692.
 29. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). *Cancer Causes Control*. 2000;11(7):653-662.
 30. Hofvind S, Skaane P, Elmore JG, Sebuodegard S, Hoff SR, Lee C. 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.
 31. Heidinger O, Heidrich J, Batzler WU, et al. Digital mammography screening in Germany: impact of age and histological subtype on program sensitivity. *Breast*. 2015;24(3):191-196.
 32. Hofvind S, Vacek PM, Skelly J, Weaver DL, Geller BM. Comparing screening mammography for early breast cancer detection in Vermont and Norway. *J Natl Cancer Inst*. 2008;100(15):1082-1091.
 33. Nederend J, Duijm LE, Voogd AC, Groenewoud JH, Jansen FH, Louwman MW. Trends in incidence and detection of advanced breast cancer at biennial screening mammography in the Netherlands: a population based study. *Breast Cancer Res*. 2012;14(1):R10.
 34. Kirsh VA, Chiarelli AM, Edwards SA, et al. Tumor characteristics associated with mammographic detection of breast cancer in the Ontario breast screening program. *J Natl Cancer Inst*. 2011;103(12):942-950.
 35. Yankaskas BC, Schell MJ, Bird RE, Desrochers DA. Reassessment of breast cancers missed during routine screening mammography: a community-based study. *AJR Am J Roentgenol*. 2001;177(3):535-541.
 36. Collett K, Stefansson IM, Eide J, et al. A basal epithelial phenotype is more frequent in interval breast cancers compared with screen-detected tumors. *Cancer Epidemiol Biomarkers Prev*. 2005;14(5):1108-1112.
 37. Gilliland FD, Joste N, Stauber PM, et al. Biologic characteristics of interval and screen-detected breast cancers. *J Natl Cancer Inst*. 2000;92(9):743-749.
 38. Sihto H, Lundin J, Lehtimäki T, et al. Molecular subtypes of breast cancer detected in mammography screening and outside of screening. *Clin Cancer Res*. 2008;14(13):4103-4110.
 39. Domingo L, Sala M, Servitja S, et al. Phenotypic characterization and risk factors for interval breast cancers in a population-based breast cancer screening program in Barcelona, Spain. *Cancer Causes Control*. 2010;21(8):1155-1164.
 40. Rayson D, Payne JI, Abdolell M, et al. Comparison of clinical-pathologic characteristics and outcomes of true interval and screen-detected invasive breast cancer among participants of a Canadian breast screening program: a nested case-control study. *Clin Breast Cancer*. 2011;11(1):27-32.