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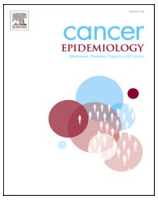

Clinical outcomes by breast cancers diagnostic modes: A comprehensive evaluation of a national breast cancer screening programme

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ABSTRACT

Introduction: Breast cancer is the leading cause of diagnosis and cancer-related death among women in almost every country worldwide. To reduce and to control breast cancer mortality, Luxembourg implemented the *Programme Mammographie*, a population-based organised programme in 1992. We aimed to compare the clinical and screening characteristics of breast cancers diagnosed in Luxembourg's eligible screening population by detection modes.

Methods: 1618 women aged 50–71 diagnosed with a first breast cancer between 2013 and 2018 were included from Luxembourg National Cancer Registry (*Registre National du Cancer, RNC)*. The detection mode (screen-detected, interval-detected, and diagnosis-detected) is determined by linking RNC data with 144,270 participations in the *Programme Mammographie* between 2011 and 2018.

Results: Screen-detected breast cancers were diagnosed at younger ages, more often found *in situ*, at a lower stage at diagnosis, smaller, showed less lymph node invasion, and were more frequently treated with conservative surgery than diagnosis-detected. Interval-detected cases had the lowest proportion of *in situ* cancers and displayed distinct molecular subtypes usually considered as more aggressive. Cancers found after the initial round of participation had worse prognosis than those found after subsequent rounds. Interval cancers diagnosed during the second year had worse prognosis than those diagnosed in the first year after participation. The best prognosis was identified in screen-detected cases whose participation was on time regarding the penultimate, and the worst in diagnosis-detected with no participation over the period.

Conclusions: Regular participation in the *Programme Mammographie* is associated with earlier detection and less advanced forms of breast cancer at diagnosis. However, healthier behaviors among screening participants might also contribute to these outcomes. The indicators produced supports public health policies to further increase its level of effectiveness.

1. Introduction

Breast cancer is the most diagnosed cancer and the leading cause of cancer deaths among women worldwide, in the European Union and in Luxembourg [1]. Meta-analyses of randomized clinical trials (RCTs) conducted in the late 1970s and early 1980s demonstrated that early detection through breast cancer screening could potentially reduce breast cancer mortality. The intensity of this reduction is heterogeneous between meta-analyses due to variations in included trials, follow-up durations, outcome definitions, and methods used [2–6].

Evidence gathered from these RCTs have been used to support the implementation of widespread opportunistic breast cancer screening (*i.e.*, initiated by women and/or health professional) in Europe. Organised breast cancer screening programmes have later been introduced mainly due to their ability to meet higher quality standards and reduce inequities in access [7]. The *Programme Mammographie* (PM), a national population-based organised breast cancer screening programme, was implemented in Luxembourg in 1992, alongside opportunistic

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screening. Women aged between 50 and 69 years old, residents and affiliated to the National Health Insurance are invited to perform a free of charge biennial two-view mammography in one of the accredited centres in Luxembourg. A systematic blinded double reading is performed by radiologists. The invitation coverage is close to 100 % [8].

The published RCTs were led in only five countries, over 40 years ago, and were often limited to specific geographical areas and dedicated clinical centres. Furthermore, significant differences exist between these RCTs and the current public health policies and methods framing breast cancer screening programmes. It is noteworthy that they also vary significantly from one country to another and change over time [9]. The relevance of early RCTs should therefore be questioned upon ensuring and quantifying the effectiveness of real-life modern screening programmes. Clear evidence-based benefits of breast cancer screening need to be continuously demonstrated through high-quality monitoring and evaluation. It is the only possible path to ensure its effectiveness, pertinence and continuous improvement. It is equally necessary for the delivery of a reliable and trustworthy information directed to the eligible population.

The possibility to link individual data from screening programmes with cancer registries for evaluation purposes has been largely overlooked. [9–14]. *Although data linkage is routine in some countries for quality monitoring, such as tracking interval cancer rates, this has not been systematically done in Luxembourg until recently* Using this methodology with data from the PM and the *Registre National du Cancer* (RNC), Luxembourg's national population-based cancer registry, the aim of this study was to compare clinical and screening characteristics of breast cancers diagnosed in Luxembourg's eligible screening population by detection modes. This study examines breast cancer outcomes based on different detection modes, referring to whether cancers were detected through organized screening, as interval cancers, or outside of the screening program (diagnosis-detected).

2. Methods

This article was written following the STROBE guidelines [15].

2.1. Registre National du Cancer (RNC)

Luxembourg's National Cancer Registry (*Registre National du Cancer*, RNC) is a high-resolution population-based cancer registry whose registration started in 2013. Data from all 1621 women aged 50–71 (maximum recommended age for participation plus an interval of follow-up) diagnosed with a first breast cancer (*in situ* or invasive) detected and/or treated in Luxembourg between 2013 and 2018 were included in this study. In case of simultaneous breast cancers, only the case with the higher stage at diagnosis was kept. Three cases were excluded because of missing data on laterality, needed to determine the detection mode. The final dataset included 1618 women. We collected the date of incidence, age at diagnosis, stage at diagnosis according to the TNM 8 classification (including *in situ*), type of surgery, molecular subtype, size of the tumours, and lymph nodes status.

2.2. Programme Mammographie (PM)

The PM is a national population-based organised cancer screening programme. In order to define cancer cases by detection mode, it was necessary to look at the participation history within at least two years preceding their diagnosis. In order to match PM data with RNC data, we included 144,270 participations occurring between 2011 and 2018, corresponding to 58,858 eligible women. Participation rate over this period was around 60 %, with a slight decrease over time. For each participation, we collected the dates of the mammography exams and their results.

2.3. Data linkage

PM and RNC data were linked after using a pseudonymized identifier created with the same algorithm in both datasets. Three participations returned errors during the process of generating the pseudonymized identifiers in the screening data and were excluded.

2.4. Mode of detection

Cases confirmed during the two-year interval following a mammography exam were defined as cases in current screeners. Among them, cases were considered as screen-detected if the mammography exam was positive for the diagnosed breast, and as interval-detected if it was negative. Interval-detected cases were further stratified based on whether they were diagnosed in the first or second year after the exam. In both screen-detected and interval-detected cases, the detection can occur after the first screening exam (the initial round) or in a subsequent round. Among subsequent rounds, the participation was considered as on time if the penultimate exam was performed within the interval (2 years) plus a 3-month margin, and delayed otherwise. Cancers i.e. detected outside the interval after a screening exam were defined as diagnosis-detected. They were further stratified based on whether women had undergone at least one mammography exam during the period or not. Cancers were also classified as 'never attenders' for women who did not participate in the screening program during the study period and 'lapsed attenders' for those who had participated at least once but were not current at the time of diagnosis."

2.5. Analysis

We used chi-square tests when the conditions were met and Fisher's exact test otherwise. Statistical significance was considered at a p-value below 0.05. Missing data were reported in the tables but excluded from the analysis. Data management, description, and statistical tests were performed using R version 4.3.1.

3. Results

The clinical characteristics by detection mode for diagnosis-detected (n = 716, 44 %) and for current screeners (n = 902, 56 %) are described in Table 1. Current screeners were stratified in screen-detected (n = 686, 76 %) or interval-detected (n = 216, 24 %). Age groups for diagnosis-detected cases were older than screen- and interval-detected ones, while there were no differences between the two latter. Screen-detected cancers were diagnosed at earlier stages (14.4 % *in situ*, 56.6 % stage I, 23.4 % stage II, 4.6 % stage III, 1.2 % stage IV) than diagnosis-detected (8.0 % *in situ*, 37.2 % stage I, 32.1 % stage II, 14.6 % stage III, 8.0 % stage IV). Interval-detected had lowest proportion of *in situ cases (5.2 %)* and stage I-IV proportion lying between diagnosis-detected and screen-detected (46.7 %stage I, 33.8 % stage II, 10.5 % stage III, 3.8 % stage IV). Overall, 78.5 % of the surgeries were conservative. Conservative surgeries were done for 85.6 % of screen-detected, 79.8 % interval-detected and 70.6 % diagnosis-detected breast cancer cases. For diagnosis-detected, the results are stratified between those who participated at least once over the period (n = 99, 13.8 %) and those who did not (n = 617, 86.2 %).

For invasive tumours, molecular *subtypes, tumour sizes and lymph nodes status* are also described in Table 1. Among screen-detected, 4.5 % were classified as triple-negative (HR-/HER2-), while this proportion was higher in interval-detected cancers (12 %) and diagnosis-detected cancers (8 %) ($p < 0.01$). Additionally, 83 % of screen-detected cases were HR+ /HER2-, compared to 70 % of interval-detected and 78 % of diagnosis-detected cases ($p = 0.02$).

There was no statistical difference in molecular subtypes between current screeners and diagnosis-detected ($p = 0.33$). However, screen-detected cancers showed distinct molecular profiles compared to

Table 1
Clinical characteristics for diagnosis-detected and current screeners (Screen-detected and interval-detected).

All tumours	Diagnosis-detected		Current screeners		Total	p-value*
	716 (44 %)		902 (56 %)			
	Never attenders over the period 617 (86.2 %)	Lapsed over the period 99 (13.8 %)	Screen-detected 686 (42 %)	Interval-detected 216(13 %)	1618	
Age groups (years)						[C] DD-ID: 0.02
[50–53]	132 (21.4 %)	11 (11.1 %)	146 (21.3 %)	53 (24.5 %)	342 (21.1 %)	DD-SD: < 0.01
[54–57]	113 (18.3 %)	16 (16.2 %)	132 (19.2 %)	50 (23.1 %)	311 (19.2 %)	SD-IC: 0.39
[58–61]	109 (17.7 %)	16 (16.2 %)	136 (19.8 %)	37 (17.1 %)	298 (18.4 %)	NA-LA: 0.03
[62–65]	95 (15.4 %)	15 (15.2 %)	147 (21.4 %)	37 (17.1 %)	294 (18.2 %)	
[65–71]	168 (27.2 %)	41 (41.4 %)	125 (18.2 %)	39 (18.1 %)	373 (23.1 %)	
Stage at diagnosis			[1]			[C] DD-ID: 0.02
In situ	50 (8.3 %)	6 (6.2 %)	98 (14.4 %)	11 (5.2 %)	165 (10.4 %)	DD-SD: < 0.01
I	213 (35.5 %)	46 (47.4 %)	384 (56.5 %)	98 (46.7 %)	741 (46.7 %)	[F]SD-IC: < 0.01
II	188 (31.3 %)	36 (37.1 %)	159 (23.4 %)	71 (33.8 %)	454 (28.6 %)	NA-LA: < 0.01
III	94 (15.7 %)	8 (8.2 %)	31 (4.6 %)	22 (10.5 %)	155 (9.8 %)	
IV	55 (9.2 %)	1 (1.0 %)	8 (1.2 %)	8 (3.8 %)	72 (4.5 %)	
Invasive NA	17	2	6	6	31	
Surgery						[C] DD-ID: 0.01
Conservative	367 (69.1 %)	75 (78.9 %)	570 (85.6 %)	162 (79.8 %)	1174 (78.5 %)	DD-SD: < 0.01
Not conservative	164 (30.9 %)	20 (21.1 %)	96 (14.4 %)	41 (20.2 %)	321 (21.5 %)	SD-IC: 0.06
NA	86	4	20	13	123	NA-LA: 0.07
Invasive tumours			588 (40.5 %)	205 (14.1 %)	1453	
Subtypes						[C] DD-ID: 0.12
HR-/HER2-	46 (8.7 %)	5 (5.7 %)	25 (4.5 %)	23 (11.5 %)	99 (7.2 %)	DD-SD: 0.02
HR+ /HER2-	410 (77.5 %)	70 (79.5 %)	461 (82.5 %)	139 (69.5 %)	1080 (78.5 %)	SD-IC: < 0.01
HR-/HER2 +	23 (4.3 %)	2 (2.3 %)	14 (2.5 %)	10 (5.0 %)	49 (3.6 %)	NA-LA: 0.56
HR+ /HER2 +	50 (9.5 %)	11 (12.5 %)	59 (10.5 %)	28 (14.0 %)	148 (10.8 %)	
NA	38	5	29	5	77	
Size			[2]			[C] DD-ID: 0.06
≤ 10 mm	99 (19.4 %)	21 (24.7 %)	192 (35.7 %)	33 (17.6 %)	345 (26.1 %)	DD-SD: < 0.01
> 10 & ≤ 20 mm	172 (33.7 %)	37 (43.5 %)	229 (42.6 %)	84 (44.7 %)	522 (39.5 %)	SD-IC: < 0.01
> 20 mm	239 (46.9 %)	27 (31.8 %)	117 (21.7 %)	71 (37.8 %)	454 (34.4 %)	NA-LA: 0.03
NA	57	8	50	17	132	
Lymph nodes status						[C] DD-ID: 0.01
Not invaded	277 (57.8 %)	64 (73.6 %)	428 (76.6 %)	135 (70.7 %)	904 (68.7 %)	DD-SD: < 0.01
Invaded	202 (42.2 %)	23 (26.4 %)	131 (23.4 %)	56 (29.3 %)	412 (31.3 %)	SD-IC: 0.13
Not examined or NA	88	6	29	14	137	NA-LA: < 0.01

[C] Chi-squared test,
[F] Fisher's Exact Test
[*] Without missing data,

interval-detected and diagnosis-detected cases (p = 0.02). Tumours were smaller for screen-detected (79 % < 20 mm) than interval- (63 % < 20 mm) and diagnosis-detected (55 % < 20 mm) cases. Lymph nodes were more often invaded for diagnosis-detected (39.3 %) compared with screen-detected (23.4 %), and interval-detected (29.3 %).

Results for cases found after the initial round (interval-detected: n = 36; screen-detected: n = 148) or after subsequent rounds (interval-detected: n = 180; screen-detected: n = 538) are described in Table 2. In the initial round, screen-detected were globally having a more advanced stage than in subsequent rounds. However, no stage IV was screen-detected in the initial round, but 1.5 % in subsequent rounds. Conservative surgery in interval-detected and screen-detected cases was lower for those diagnosis in the first year compared to the second year. For invasive tumours, screen-detected tumours were larger in the initial round than in subsequent rounds. For interval-detected tumours, the sizes were larger in the second year than in the first year.

Results for on time (interval-detected: n = 133; screen-detected: n = 396) or delayed participations (interval-detected: n = 17; screen-detected: n = 105) for women with sufficient follow-up are detailed in Table 3. For the screen-detected delayed group, the mean delay beyond the regular 2-year interval was 3 months. Early stages were highest among screen-detected cases with on time participation, where the proportion of *in situ* reached 17.0 % compared to 6.7 % for those with delayed participation.

For interval-detected, the results are stratified for the first (n = 82, 38 %) or second year after the screening exam (n = 134, 62 %) in Table 4. Among diagnosis-detected cases, stages were earlier for women who had been screened at least once over the period, with 10 % of stages III and IV, compared with 25 % for those who have not. The larger tumours were observed among diagnosis-detected who had no participation over the period. Among diagnosis-detected, the largest proportion was found for those who have no participation over the period (42 %). Finally, Table 5 summarises our results for the screen-detected cancers in relation to the European recommendations.

4. Discussion

This study represents the most comprehensive evaluation of breast cancer cases among the population eligible for screening in Luxembourg, considering the detection mode. It is also the first instance in which data from the national population-based cancer registry has been utilized for this purpose. Earlier published studies from the country mainly focused on breast cancer tumour sizes [16–18] and lymph node status, mostly in screen-detected cases [17,18]. Due to differences in periods, data sources, eligible populations and definitions, direct comparisons with these studies are challenging. However, compared to national results published before the PM implementation (1985–1987), the percentage of *in situ* breast tumours detected increased (1 % versus 10 %), and the percentage of invasive tumours with a tumour size above 20 mm at diagnosis decreased (57 % vs. 31 %). Part of these differences might be explained by the PM effect.

Our results indicate that screen-detected breast cancers were diagnosed at a younger age, more often found *in situ*, at a lower stage at diagnosis, smaller in size, showed less lymph node invasion, and were

Table 2
Clinical characteristics by detection mode for interval-detected and screen-detected in the initial or subsequent rounds.

	Interval-detected (n = 216)		Screen-detected (n = 686)		p-value*
	Initial round	Subsequent round	Initial round	Subsequent round	
All tumours	36 (4 %)	180 (16.4 %)	148 (20.0 %)	538 (59.6 %)	
Age groups (years)					[C] < 0.01
[50–53]	33 (91.7 %)	20 (11.1 %)	103 (69.6 %)	43 (8.0 %)	
[54–57]	1 (2.8 %)	49 (27.2 %)	21 (14.2 %)	111 (20.6 %)	
[58–61]	0 (0 %)	37 (20.6 %)	13 (8.8 %)	123 (22.9 %)	
[62–65]	1 (2.8 %)	36 (20.0 %)	7 (4.7 %)	140 (26.0 %)	
[65–71]	1 (2.8 %)	38 (21.1 %)	4 (2.7 %)	121 (22.5 %)	
Stage at diagnosis					[F] < 0.01
In situ	1 (2.9 %)	10 (5.7 %)	17 (11.6 %)	81 (15.2 %)	
I	16 (45.7 %)	82 (46.9 %)	68 (46.6 %)	316 (59.2 %)	
II	11 (31.4 %)	60 (34.3 %)	47 (32.2 %)	112 (21.0 %)	
III	6 (17.1 %)	16 (9.1 %)	14 (9.6 %)	17 (3.2 %)	
IV	1 (2.9 %)	7 (4.0 %)	0 (0 %)	8 (1.5 %)	
Invasive NA	1	5	2	4	
Surgery					[C] 0.18
Conservative	27 (77.1 %)	135 (80.4 %)	116 (82.7 %)	454 (86.6 %)	
Not conservative	8 (22.9 %)	33 (19.6 %)	26 (18.3 %)	70 (13.3 %)	
NA	1	12	6	14	
Invasive tumours	35 (4.4 %)	170 (21.4 %)	131 (16.5 %)	457 (57.6 %)	
Subtypes					[F] 0.05
HR-/HER2-	4 (11.8 %)	19 (11.4 %)	6 (4.7 %)	19 (4.4 %)	
HR+ /HER2-	24 (70.6 %)	115 (69.3 %)	97 (75.8 %)	364 (84.5 %)	
HR-/HER2 +	2 (5.9 %)	8 (4.8 %)	3 (2.3 %)	11 (2.6 %)	
HR+ /HER2 +	4 (11.8 %)	24 (14.5 %)	22 (17.2 %)	37 (8.6 %)	
NA	1	4	3	26	
Size					[C] < 0.01
≤ 10 mm	7 (22.6 %)	26 (16.6 %)	33 (27.5 %)	159 (38.0 %)	
> 10 & ≤ 20 mm	12 (38.7 %)	72 (45.9 %)	48 (40.0 %)	181 (43.3 %)	
> 20 mm	12 (38.7 %)	59 (37.6 %)	39 (32.5 %)	78 (18.7 %)	
NA	4	13	11	39	
Lymph nodes status					[C] 0.10
Not invaded	22 (66.7 %)	113 (71.5 %)	89 (70.6 %)	339 (78.3 %)	
Invaded	11 (33.3 %)	45 (28.5 %)	37 (29.4 %)	94 (21.7 %)	
Not examined or NA	2	12	5	24	

[*] Among screen-detected only & without missing data,
[C] Chi-squared test,
[F] Fisher's Exact Test

more frequently treated with conservative surgery compared to diagnosis-detected. Interval-detected breast cancers had the lowest proportion of *in situ* cancers. All other clinical characteristics of interval-detected breast cancers were between the characteristics found for screen-detected and diagnosis-detected breast cancers. As expected, cancers detected in the initial round had a worse prognosis than those detected in subsequent rounds [19–22] because the initial round aims to detect all cancers that might have occurred before the first participation. This participation and its timing are thus particularly important, as a delay would worsen the prognosis of prevalent cancers. Even if screen-detected cancers have the best prognosis characteristics overall, some were detected at an advanced stage (6 % were stage III or IV). We had no information on whether women were symptomatic at screening or not, but it needs to be made clear that women should consult their healthcare provider whenever the first symptoms appear. Screen-detected cases with on-time participation had the best prognosis of all. Among diagnosis-detected, women who participated at least once over the study period had a better prognosis than those who did not. All highlighted indicators suggest that regular participation in and/or cancer detection through screening is associated with earlier detection and less against advanced forms of breast cancer at diagnosis, though this may be influenced by the overall health behaviours of participants.

The performance of a cancer screening programme is mainly limited by the adherence of the eligible population and interval cancers. The level of adherence determines the total number of individuals who are expected to benefit from screening in the event of a cancer diagnosis. Cancers detected in women who did not participate over the study period had the worst prognosis of all groups, with a quarter diagnosed at stage III or IV, and nearly half of the invasive tumours being larger than 20 mm. On one hand, the observed difference compared to the other groups is probably underestimated, as some women who have not participated in the PM might have been diagnosed through opportunistic screening. Published studies have shown that, regarding clinical characteristics, diagnosis through opportunistic or organised screening produces close results [23–26]. This hypothesis is strengthened by the non-negligible amount of *in situ* cancers in this group that are rarely detected in the absence of screening. Unfortunately, data on opportunistic screening are not available in Luxembourg. On the other hand, the observed difference might be overestimated due to a self-selection bias [27]. By definition, all PM participations are the result of individual decisions. It has been argued that the factors associated with this decision to participate might be associated with better cancer outcomes, regardless of screening. Another element that could lead to a misestimation of the difference is over diagnosis. It refers to the detection of cancers through screening (organised or opportunistic) that would not have caused harm in a person's lifetime if left untreated. Quantifying over diagnosis is a challenging task, and ongoing debates trace back to the randomized clinical trials mentioned in the introduction [28]. Multiple methods have been proposed, leading to highly heterogeneous results ranging from 0 % to 54 % [29].

Interval-detected cancers accounted for 24 % of the cancers detected in current screeners, which is consistent with a review reporting a range of 17–30 % [30]. They demonstrated clear intermediate outcomes between screen- and diagnosis-detected cancers. Most studies have compared screen- and interval-detected cancers, generally agreeing on a poorer prognosis for the latter [19,20,30–40]. The fewer results

Table 3
Clinical characteristics by detection mode for interval-detected and screen-detected according to penultimate screening timeliness.

	Interval-detected (n = 150)		Screen-detected (n = 501)		Total	p-value*
	On time	Delayed	On time	Delayed		
All tumours	133 (89 %)	17 (11 %)	396 (79 %)	105 (21 %)	651	
Age groups (years)						[C] 0.88
[50–53]	15 (11.3 %)	3 (17.6 %)	32 (8.1 %)	10 (9.5 %)	60 (9.2 %)	
[54–57]	38 (28.6 %)	3 (17.6 %)	84 (21.2 %)	19 (18.1 %)	144 (22.1 %)	
[58–61]	26 (19.5 %)	2 (11.8 %)	89 (22.5 %)	21 (20.0 %)	138 (21.2 %)	
[62–65]	24 (18.0 %)	4 (23.5 %)	104 (26.3 %)	29 (27.6 %)	161 (24.7 %)	
[65–71]	30 (22.6 %)	5 (29.4 %)	87 (22.0 %)	26 (24.8 %)	148 (22.7 %)	
Stage at diagnosis						[F] 0.02
In situ	6 (4.6 %)	2 (13.3 %)	67 (17.0 %)	7 (6.7 %)	82 (12.7 %)	
I	62 (47.3 %)	5 (33.3 %)	238 (60.4 %)	63 (60.6 %)	368 (57.1 %)	
II	46 (35.1 %)	6 (40.0 %)	74 (18.8 %)	29 (27.9 %)	155 (24.1 %)	
III	13 (9.9 %)	0 (0.0 %)	12 (3.0 %)	3 (2.9 %)	28 (4.3 %)	
IV	4 (3.1 %)	2 (13.3 %)	3 (1.0 %)	2 (1.9 %)	11 (1.7 %)	
Invasive NA	2	2	2	1	7	
Surgery						[C] 0.10
Conservative	103 (81.7 %)	10 (71.4 %)	341 (88.1 %)	82 (81.2 %)	536 (85.4 %)	
Not conservative	23 (18.3 %)	4 (28.6 %)	46 (11.9 %)	19 (18.8 %)	92 (14.6 %)	
NA	7	3	9	4	23	
Invasive tumours	127	15	329	98	569	
Subtypes						[F] 0.05
HR-/HER2-	16 (12.8 %)	0 (0.0 %)	15 (4.8 %)	3 (3.2 %)	34 (6.3 %)	
HR+ /HER2-	85 (68.0 %)	11 (78.6 %)	267 (86.1 %)	74 (78.7 %)	437 (80.5 %)	
HR-/HER2 +	5 (4.0 %)	1 (7.1 %)	8 (2.6 %)	2 (2.1 %)	16 (2.9 %)	
HR+ /HER2 +	19 (15.2 %)	2 (14.3 %)	20 (6.4 %)	15 (16.0 %)	56 (10.3 %)	
NA	2	1	19	4	26	
Size						[C] 0.58
≤ 10 mm	20 (16.9 %)	1 (7.7 %)	117 (38.2 %)	33 (37.5 %)	171 (32.6 %)	
> 10 & ≤ 20 mm	55 (46.6 %)	5 (38.5 %)	134 (43.8 %)	35 (39.8 %)	229 (43.6 %)	
> 20 mm	45 (36.4 %)	7 (53.8 %)	55 (18.0 %)	20 (22.7 %)	125 (23.8 %)	
NA	9	2	23	10	44	
Lymph nodes status						[C] 0.89
Not invaded	88 (72.7 %)	9 (75.0 %)	250 (79.6 %)	72 (78.3 %)	419 (77.7 %)	
Invaded	33 (27.3 %)	3 (25.0 %)	64 (20.4 %)	20 (21.7 %)	120 (22.3 %)	
Not examined or NA	6	3	15	6	30	

[*] Among screen-detected only & without missing data,
[C] Chi-squared test,
[F] Fisher's Exact Test

available to compare interval- and diagnosis-detected cancers are more mixed, even though they are generally in favour of the interval-detected [19,20,30,32,33,37]. Compared with screen-detected cancers, interval-detected displayed distinct molecular subtypes, with higher proportions of HR-, HER2 +, and triple-negative, that are often considered more aggressive and predictive of treatment ineffectiveness [13]. These differences are consistent with findings from other studies [30,35,36,39] and support the length bias theory [27]. This theory suggests that screening is more effective in detecting slow progressing cancers - and is another important piece in the puzzle of proper screening evaluation.

When considering the differences between initial and subsequent or on time and delayed participations, between interval-detected in the first or second year, or between cancers diagnosed in those who have not participated during the period and those who have at least once, it appears evident that there is more to understand about the effect of screening trajectories. Throughout their entire eligibility period, each individual will have a complex screening trajectory ranging from none to 'ideal' participation. They will impact the effectiveness of screening programmes in a way for which we have not found information in the literature. It is notable that the clinical characteristics of cancers in 'lapsed attenders' closely resemble those of screen-detected 2nd round and screen-detected delayed cases. This likely reflects the fact that 'lapsed attenders' had participated in screening at least once, leading to earlier detection of cancers compared to 'never attenders,' whose cancers tend to present at more advanced stages due to a lack of screening participation.

This study included nationwide high-quality individual data from the PM and the RNC, linked via pseudonymisation. It enabled the creation of a common language and to benefit from the expertise of both data sources and allowed the creation of specific screening groups, the analysis of participation histories and detection modes. It is particularly important for interval cancers, which are often overlooked by other study designs. Our work is further strengthened by the addition of data on diagnosed cancers, a comparison that is rarely explored in the literature. While these cases may not be as heavily impacted by screening as for current screeners, our results show that they still are. In addition, these cases will be impacted by other elements (health education, breast cancer awareness, healthcare provider training, accessibility, affordability, and prompt and effective treatment), and gathering these data enabled us to achieve a full picture of breast cancers in the eligible population over the study period. Finally, we delved into multiple clinical indicators, providing valuable insights into the intermediate outcomes of breast cancer screening and laying the groundwork for further research and improvements.

Several limitations should be considered. The overlap between screening and registry data is not perfect: the RNC collects all cases diagnosed or treated in Luxembourg, while the PM invites every insured woman and those who requested it. We were unable to differentiate between non-participants and non-invited women. Despite numerous indicators, others would have been interesting, such as breast density, hormonal replacement therapy, comorbidities, proliferation markers, opportunistic screening, grades, chemotherapy, and quality of life, as they are known to impact or be impacted by breast cancer detection mode. Another limitation lies in the sample sizes in some subgroups, especially for interval cancers and despite gathering six years of data,

Table 4
Clinical characteristics by detection mode for interval-detected cancers according to the year since participation.

	Interval detected cancers		p-value*
	First year	Second year	
All tumours	82 (38.0 %)	134 (62.0 %)	
Age groups (years)			[C]0.83
[50–53]	22 (26.8 %)	31 (23.1 %)	
[54–57]	21 (25.6 %)	29 (21.6 %)	
[58–61]	12 (14.6 %)	25 (18.7 %)	
[62–65]	14 (17.1 %)	23 (17.2 %)	
[65–71]	13 (15.9 %)	26 (19.4 %)	
Stage at diagnosis			[F]0.49
In situ	4 (5.1 %)	7 (5.3 %)	
I	43 (54.4 %)	55 (42.0 %)	
II	22 (27.8 %)	49 (37.4 %)	
III	8 (10.1 %)	14 (10.7 %)	
IV	2 (2.5 %)	6 (4.6 %)	
Invasive NA	3	3	
Surgery			[C]0.03
Conservative	67 (88.2 %)	95 (74.8 %)	
Not conservative	9 (11.8 %)	32 (25.2 %)	
NA	6	7	
Invasive tumours	78 (38.0 %)	127 (62.0 %)	
Subtypes			[F]0.50
HR-/HER2-	12 (15.8 %)	11 (8.9 %)	
HR+ /HER2-	51 (67.1 %)	88 (71.0 %)	
HR-/HER2 +	3 (3.9 %)	7 (5.6 %)	
HR+ /HER2 +	10 (13.2 %)	18 (14.5 %)	
NA	2	3	
Size			[C]0.02
≤ 10 mm	18 (26.5 %)	15 (12.5 %)	
> 10 & ≤ 20 mm	31 (45.6 %)	53 (44.2 %)	
> 20 mm	19 (27.9 %)	52 (43.3 %)	
NA	10	7	
Lymph nodes status			[C]0.60
Not invaded	53 (73.6 %)	82 (68.9 %)	
Invaded	19 (26.4 %)	37 (31.1 %)	
Not examined or NA	6	8	

* Without missing value,
C Chi-squared test,
F Fisher's exact test

Table 5
European recommendation for screened-detected cancers and measured level.

	Acceptable	Desirable	Measured
Proportion of screen-detected cancers that are invasive	90 %	80–90 %,	86 %
Proportion of invasive screen-detected cancers that are < 15 mm in size	50 %	> 50	54 %
Proportion of screen-detected cancers that are stage II+			
Initial round	NA	< 30 %	42 %
Subsequent round	25 %	< 25 %	26 %
Proportion of invasive screen-detected cancers that are ≤ 10 mm in size			
Initial round	NA	≥ 25 %	28 %
Subsequent round	≥ 25 %	≥ 30 %	38 %
Proportion of invasive screen-detected cancers that are node-negative			
Initial round	NA	> 70 %	71 %
Subsequent round	75 %	> 75 %	78 %

limiting the statistical power for some comparisons. For the same reason, we were unable to analyse mortality data. While this analysis is descriptive, focusing on clinical characteristics and detection modes, we acknowledge that a logistic regression approach could provide further insights by adjusting for potential confounders like age. We plan to explore this in future work to investigate whether treatment differences persist across detection modes after accounting for factors such as age and tumour characteristics.

In 2003, the European Union (EU) recommended to its member states that they implement national population-based organised breast cancer screening programmes [41]. Nowadays, it is applied in almost all EU countries, some for nearly 40 years and others relatively recently. EU countries differ considerably in various aspects of their screening programmes, including invitation coverage, eligible age range, participation rate, screening methods, screening intervals, and overall organisation. In the meantime, their evaluations remain very limited in most countries [9]. To help standardize measures and monitoring, the European Commission proposed guidelines and targets for mammography-based screening [14] that are sometimes used [21, 42–47]. Overall, our study's results align with the proposed targets, however, the significant disparities observed between the various screening programmes that have been evaluated suggest heterogeneity in the performances and results. Similar findings have been reported in studies comparing directly breast cancer screening programmes across different countries [47,48]. Despite being implemented with the aim of ensuring an equal access to every individual, participation in organised cancer screenings is known to still be unequal, with, here again, unexplained heterogeneity between countries [49–54]. The level of inequities in participation will partly be a consequence of the organisation as well as one of the drivers of screening effectiveness. Progressing towards more comprehensive systems that allow for monitoring and comparison of results between countries would enable the identification of the best screening practices and the evidence-based improvement of screening policies and effectiveness at large scales.

5. Conclusion

Our results suggest that detection of cancer cases through organised breast cancer screening increases the likelihood of early cancer diagnosis. More regular or recent participations in screening also appears to increase this probability. International collaborations and implementation of standard methodologies are crucial for creating more comparable screening performance indicators. This would enhance our understanding of how screening works, and how we could optimize its effectiveness based on the evidence, ultimately leading to improvement in early cancer detection.

CRediT authorship contribution statement

Backes Claudine: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rollet Quentin:** Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Robert Isabelle:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Couffignal Sophie:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Data curation, Conceptualization. **Lorin Fanny:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Rivero Yaiza:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

Ethics approval and consent to participate

The data used in this study were pseudonymised, and did not require any additional ethical approval beyond that already granted to the *Registre National du Cancer*.

Author contributions

All authors participated in study conception, design, result

interpretation and manuscript revision. CB, SC, IR and FL insured data acquisition and control. Data analysis and manuscript preparation were done by QR. All authors gave final approval for this version to be published.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data used is restricted. Requests can be made to the *Registre National du Cancer* to gain access.

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