



Annual mammography at age 45–49 years and biennial mammography at age 50–69 years: comparing performance measures in an organised screening setting

Lauro Bucchi¹ · Alessandra Ravaoli¹ · Flavia Baldacchini¹ · Orietta Giuliani¹ · Silvia Mancini¹ · Rosa Vattiato¹ · Fabio Falcini^{1,2} · Paolo Giorgi Rossi³ · Cinzia Campari⁴ · Debora Canuti⁵ · Enza Di Felice⁶ · Priscilla Sassoli de Bianchi⁶ · Stefano Ferretti⁷ · Nicoletta Bertozzi⁶ · on behalf of the Emilia-Romagna Region Workgroup for Mammography Screening Evaluation

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Abstract

Objective To compare the results of 5 years of annual mammography screening at age 45–49 with the results of 5 years of biennial screening at age 50–54 and 55–69.

Methods In an Italian screening programme, data from 1,465,335 mammograms were analysed. Recall rates, invasive assessment rates, surgical biopsy (including excisional biopsy and definitive surgical treatment) rates, and cancer detection rates were calculated for the first screen (first) and, cumulatively, for the second and subsequent screens (second+).

Results The rate ratios between younger women and the two groups of older ones were (in parentheses, original figures per 1000 mammograms if not otherwise specified): recall rate: first 1.11 (103.6 vs. 93.5) and 1.11 (vs. 93.2), second+ 2.10 (208.9 vs. 99.7) and 2.77 (vs. 75.5); invasive assessment rate: first 0.94 (23.0 vs. 24.5) and 0.94 (vs. 24.6), second+ 1.63 (35.8 vs. 22.0) and 1.56 (vs. 23.0); surgical biopsy rate: first 0.68 (5.9 vs. 8.6) and 0.45 (vs. 13.2), second+ 1.35 (11.5 vs. 8.5) and 0.88 (vs. 13.0); total detection rate: first 0.63 (4.3 vs. 6.7) and 0.37 (vs. 11.7), second+ 1.30 (8.9 vs. 6.8) and 0.74 (vs. 12.0); total positive predictive value of surgical biopsy: first 0.93 (72.8% vs. 78.0%) and 0.82 (vs. 88.9%), second+ 0.96 (77.2% vs. 80.5%) and 0.83 (vs. 92.7%).

Conclusion Younger women experienced two to threefold higher cumulative recall rates at second+ screens and limited differences in surgical biopsy rate. Albeit encouraging, these results must be completed with further investigation, especially on interval cancer incidence.

Key Points

- At repeated screens, cumulative recall rate was two- to threefold higher for younger women.
- Differences in cumulative surgical referral and surgical biopsy rates were moderate.
- Differences in positive predictive value of surgical biopsy were particularly small.

Keywords Mass screening · Mammography · Breast neoplasms · Premenopause · Biopsy

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✉ Lauro Bucchi
lauro.bucchi@irst.emr.it

¹ Romagna Cancer Registry, Romagna Cancer Institute (Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, IRST, IRCCS), Meldola, Forlì, Italy

² Local Health Authority, Forlì, Italy

³ Epidemiology Unit, Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Reggio Emilia, Italy

⁴ Cancer Screening Unit, Azienda Unità Sanitaria Locale – IRCCS di Reggio Emilia, Reggio Emilia, Italy

⁵ Local Health Authority, Rimini, Italy

⁶ Department of Health, Regional Administration, Emilia-Romagna Region, Bologna, Italy

⁷ University of Ferrara and Local Health Authority, Ferrara, Italy

Abbreviations

DCIS	Ductal carcinoma in situ
ECIBC	European Commission Initiative on Breast Cancer
FNA	Fine-needle aspiration
GISMa	Italian Group for Mammography Screening
NCB	Needle core biopsy
PPV	Positive predictive value
VAB	Vacuum-assisted biopsy

Introduction

The benefit of mammography screening for women under 50 years of age is considered less, and less certain, than for older ones. Since 2006, the European guidelines have recommended that organised mammography screening programmes be targeted at women aged 50–69 years [1]. Screening recommendations from some major medical agencies have substantially supported this age restriction [2, 3]. In Europe, biennial screening programmes for women aged 40–49 or 45–49 years have so far been introduced only in Iceland, the Czech Republic, Hungary, and some regional areas [4]. In the UK, the target age range is currently being extended but with the age threshold set at 47 years [5].

In 2017, the situation has changed. For women aged 45–49 years, the European Commission Initiative on Breast Cancer (ECIBC) Guideline Development Group has issued a conditional recommendation for mammography screening in the context of organised programmes [6]. The extent to which this will influence public health screening policies in Europe remains to be seen, but it is likely that the new guidelines will interact synergistically with the American Cancer Society guidelines of 2015, which state that average-risk women should begin having annual mammograms at age 45 years, and can change to having mammograms every other year beginning at age 55 years [7].

For organised screening programmes, however, the choice of the screening interval for women aged 45–49 years would be a challenging issue. The ECIBC Guideline Development Group has made no recommendation at all [6]. In the new European guidelines, carrying out evaluations of time intervals is identified as a research priority. Specifically, they recommend that future evaluations of screening services for women aged 45–49 years provide their results in the context of evolving diagnosis and treatment protocols and in relation to the screening interval.

This is certainly necessary, as published studies on the performance measures of an annual screening protocol for women aged 45–49 years in a public health setting have so far been anecdotal [8]. This article is a contribution to bridge this knowledge gap. In an administrative region of Italy, women aged 45–49 years have been invited to participate annually in an organised screening programme since 2010. We report here

a study of recall rates, surgical referral rates, surgical biopsy rates, detection rates of breast cancer, and other important performance measures of annual screening in this age group.

Materials and methods

Background: Italian screening guidelines for women under 50 years of age

According to the Italian Group for Mammography Screening (GISMa) guidelines of 2006, the extension of organised programmes to the age 40–49 years—albeit not recommended—can be taken into consideration provided that coverage of women aged 50–69 years has been completed; budget is sufficient; priority is given to the age group 45–49 years; information on pros and cons of screening at this age is given; mammography is offered annually, taken in two views, and double-read; and the process is monitored [9].

Setting

Since 1995–1997, depending on the health care district, the Emilia-Romagna Region (northern Italy) has been targeted by a free-of-charge, two-yearly, two-view, double-read mammography screening programme for women aged 50–69 years. The programme is run by 11 health care district screening units. Methods and organisation are reported elsewhere [10, 11].

In 2009, for the first time in Italy, the Regional Administration extended the target age of the programme to include women aged 45–49 years (and 70–74 years) [12].

In 2013 (the mid-year of the study period, see the “Time period” section), the number of interpreting radiologists in the screening centres ranged between 2 and 10 (median, 6), their years of experience in reading mammograms between 1 and 31 (median, 11), the percentage of working time they dedicated to breast radiology between 20 and 100 (median, 100), and their annual screening mammogram reading volume between 1500 and 25,000 (median, 8500).

In the same year, pooling first and subsequent screens, the screening units reported a range of 3–9% for the recall rate, 4–8 per 1000 for the surgical biopsy rate (including excisional biopsy and definitive surgical treatment), and 3–7 per 1000 for the total detection rate of ductal carcinoma in situ (DCIS) and invasive breast cancer. These data are for women aged 45–74 years.

Currently (November 2018), there are 49 radiology facilities and two mobile mammography units providing screening mammograms.

During the entire study period, digital breast tomosynthesis was not yet in use at any of the screening centres (except for research purposes).

Time period

Women aged 45–49 years began to be invited in 2010. Their enrolment increased progressively and was completed in 2014 [12]. We evaluated the performance of screening among women invited in the 5-year period between 2011 and 2015. The year 2010 was excluded from the study due to the low volume of invitations and a possible selection bias.

Data sources

The greater part of data for the study were taken from the annual national surveys conducted by the GISMa and the National Centre for Screening Monitoring. These surveys collect aggregate data from local screening units. In many studies, their quality for statistical purposes has been shown to be acceptable [13, 14]. Data are gathered by trained personnel and submitted with a standard electronic form. Before being forwarded to the GISMa, the data collected in the Emilia-Romagna Region are subjected to systematic checks at the Department of Health of the Regional Administration. During the study period, pooling first and subsequent screens, the proportion of missing data was 2% for assessment, 5% for pT status and 5% for pN status.

The interscreening intervals were calculated using the regional database of screening mammography records. The proportion of screen-detected cancers with preoperative cytological and histological diagnoses (C5 and B5) [6] was calculated using the original regional data from a national audit of surgical treatment of screen-detected lesions conducted in 2015, in which the first and subsequent screens were pooled [15].

The professional characteristics of screening radiologists (see the “Setting” section) were determined using the original regional data from a national survey conducted by the GISMa in 2013 [16].

Objectives and rationale

The general objective of the study was to assess the standard performance measures of screening among women undergoing 5 years of annual mammography between age 45 and 49 as compared with women undergoing 5 years of biennial mammography in the age range 50–54 and 55–69. More specifically, we aimed, first, at reporting descriptively the performance measures in the three age groups and, second, at calculating their ratio comparing younger women vs. both groups of older ones. Our rationale was that this comparative approach would allow for a more direct understanding of the results of annual screening between 45 and 49 years of age.

Design

We considered that, numbering from 1 to 5 the years during which a woman aged 45 (in year 1) receives an annual mammogram, a woman aged 50 years or older is screened in years 1, 3, and 5. This suggested that younger and older women can be compared for the results of the first screen and, then, for the cumulative results of their subsequent screens over an equal 4-year time period. In this way, we made allowance for the fact that women aged 45–49 years are exposed to the process twice as often as older ones [17]. The 5-year cumulative rates were also calculated as summary measures.

In all age groups, the recall rate, the non-invasive and invasive assessment rates, the surgical referral and surgical biopsy rates, and the detection rates of benign breast lesion and of breast cancer by pT and pN status per 1000 first-screen mammograms and, separately, per 1000 mammograms at second and subsequent screens were calculated as average values of the study period. These values were used to calculate the cumulative rates. Surgical referral was defined as referral for excisional biopsy or definitive surgical treatment. Surgical biopsy was defined as excisional biopsy or definitive surgical treatment.

Like the above rates, the DCIS to invasive cancer ratio, the pT and pN percent distribution of invasive cancers, the percent positive predictive value (PPV) of mammography, surgical referral, and surgical biopsy for DCIS and invasive cancer, and the percent proportion of cancers undergoing breast-conserving surgery were separately calculated for women at their first and subsequent screens as average values of the study period. These measures, describing the clinical characteristics of screen-detected abnormalities, did not undergo any further treatment.

Data analysis

Women of all ages presenting to screening centres who reported a recent (< 12 months) spontaneous mammography were not screened nor included in the number of women invited. Women who were unreachable (letter returned to sender) were considered non-attenders. The participation rate was defined as the proportion of invited women undergoing screening mammography.

The cumulative rates were calculated using standard methods [18]. Women aged 45–49 years were compared with older ones by calculating the ratios of rates and percent proportions and the 95% confidence intervals (CI) around them. These were estimated using standard methods [19].

Ethical issues

In compliance with the Italian legislation, women presenting to screening centres were not asked for their informed consent

to undergo mammography. The study protocol was approved by the Ethics Committee at the Romagna Cancer Institute (ID: IRST100.37).

Results

Number of invitations and mammograms

On 1 January 2011, the target population included 176,440 women aged 45–49 years; 156,026 women aged 50–54 years; and 407,155 women aged 55–69 years.

During the study period, this population received 323,371 invitations to the first screen and 1,842,509 invitations to the second and subsequent screens, for a total of 2,165,880.

The upper row of Table 1 shows the total number of screening mammograms performed. The participation rate by age group was 71.9%, 86.4%, and 94.1% at the first screen and 64.2%, 62.6%, and 68.7% at the second and subsequent screens, respectively.

The frequency of testing by age group was very near to the nominal one, with a median interscreening interval of 391 days, 746 days, and 744 days, respectively.

Recall rate, assessment rate, surgical referral rate, surgical biopsy rate, and detection rate

The second and subsequent rows of Table 1 show the number of recalls for assessment, assessments performed by type,

Table 1 Number of screening mammograms, recalls, assessments by type, surgical referrals and surgical biopsies, and detected benign and malignant breast lesions at the first screen and at the second and

subsequent screens, by woman's age group. Emilia-Romagna Region mammography screening programme (2011–2015)

	First screen				Second and subsequent screens				Total
	45–49	50–54	55–69	Total	45–49	50–54	55–69	Total	
Screening mammograms	174,657	44,801	26,761	246,219	345,235	228,106	645,775	1,219,116	1,465,335
Recalls	18,102	4187	2494	24,783	18,032	11,370	24,393	53,795	78,578
Assessments									
Non-invasive assessment	13,732	2959	1695	18,386	14,755	8731	16,622	40,108	58,494
Invasive assessment									
FNA	2184	654	317	3155	1544	1180	3637	6361	9516
NCB, VAB	1838	442	342	2622	1549	1330	3778	6657	9279
Total invasive assessments	4022	1096	659	5777	3093	2510	7415	13,018	18,795
Total assessments	17,754	4055	2354	24,163	17,848	11,241	24,037	53,126	77,289
Surgical referrals	1091	410	377	1878	1056	1057	4423	6536	8414
Surgical biopsies	1026	387	352	1765	991	968	4192	6151	7916
Detected benign breast lesions	243	69	38	350	191	162	264	617	967
Detected breast cancers									
DCIS	225	88	55	368	187	191	653	1031	1399
Invasive cancer									
pT1mic-a-b	175	79	90	344	197	206	1310	1713	2057
pT1c	222	83	96	401	244	259	1303	1806	2207
pT2–4	97	41	59	197	97	99	460	656	853
pTX, missing pT information	25	11	10	46	37	21	146	204	250
pN-negative	346	148	165	659	399	414	2455	3268	3927
pN-positive	153	52	79	284	137	156	603	896	1180
pNX, missing pN information	13	7	7	27	39	15	160	214	241
Total invasive cancers*	522	214	258	994	578	588	3234	4400	5394
Total breast cancers*	747	302	313	1362	765	779	3887	5431	6793

FNA fine-needle aspiration; NCB needle core biopsy; VAB vacuum-assisted biopsy; DCIS ductal carcinoma in situ

Recall indicates recall for further assessment. Non-invasive assessment indicates one or more among ultrasound, diagnostic mammography, breast physical examination, and other tests without pathologic evaluation. Surgical referral indicates referral for excisional biopsy or definitive surgical treatment. Surgical biopsy indicates excisional biopsy or definitive surgical treatment. Second and subsequent screens indicate the second, third, fourth, and fifth annual screen for women aged 45–49 years, and the second and third biennial screen for women aged 50–54 years and 55–69 years

*Including pTX and pNX invasive cancers and invasive cancers with missing pT and pN information

surgical referrals and biopsies, and benign and malignant screen-detected lesions in the three age groups.

Table 2 shows the recall rate, the assessment rates, the surgical referral rate, the surgical biopsy rate, and the detection rates per 1000 screened women at the first screen and at the second and subsequent screens. The response rate to recall (not shown) was >94% at the first screen and >98% at the second and subsequent screens in all three groups.

For all of the rates in Table 2, Table 3 shows the ratio between younger women and women aged 50–54 years and 55–69 years. At the first screen, the recall rate was 11% higher for younger women compared with both groups of older ones. The non-invasive assessment rate was moderately higher, with a ratio of 1.19 vs. women aged 50–54 years and 1.24 vs. women aged 55–69 years. With respect to the invasive assessment rate, no excess was observed (ratio, 0.94 vs. both groups of older women). The surgical referral rate was markedly lower, with a ratio of 0.68 and 0.44, respectively. The same was observed for the surgical biopsy rate (ratio, 0.68 and 0.45).

The detected prevalence of DCIS was one-third lower compared with both groups of older women, with a ratio of 0.66 and 0.63, respectively. The yield of invasive cancer too was less, with a ratio as low as 0.31 vs. women aged 55–69 years.

At second and subsequent screens, younger women experienced a two- to threefold higher recall rate, with ratios of 2.10 and 2.77. This led to a larger increase in non-invasive assessment rate, with the invasive assessment rate being only approximately 60% higher than among both groups of older women (ratio, 1.63 and 1.56, respectively). The excess of surgical referrals was even less pronounced and was found only when comparing younger women with women aged 50–54 years, with a ratio of 1.32. Taking women aged 55–69 years as a reference, younger women had an approximately 10% lower surgical referral rate (ratio, 0.89). Virtually the same ratios were found for the surgical biopsy rate. In terms of yield of disease, the situation was similar. The total detection rate of cancer among women aged 45–49 years was 30% higher than among women aged 50–54 years and 26% lower

Table 2 Recall rate, assessment rate by type, surgical referral and surgical biopsy rates, and detection rate of breast cancer at the first screen and homologous cumulative rates at the second and subsequent screens, by woman’s age group. All rates are per 1000 screening mammograms. Emilia-Romagna Region mammography screening programme (2011–2015)

	Rate at the first screen			Cumulative rate at the second and subsequent screens		
	45–49	50–54	55–69	45–49	50–54	55–69
Recall rate	103.6	93.5	93.2	208.9	99.7	75.5
Assessment rates						
Non-invasive assessment	78.6	66.0	63.3	171.0	76.6	51.5
Invasive assessment						
FNA	12.5	14.6	11.8	17.9	10.3	11.3
NCB, VAB	10.5	9.9	12.8	17.9	11.7	11.7
Total invasive assessment	23.0	24.5	24.6	35.8	22.0	23.0
Surgical referral rate	6.2	9.2	14.1	12.2	9.3	13.7
Surgical biopsy rate	5.9	8.6	13.2	11.5	8.5	13.0
Detection rate of benign breast lesion	1.4	1.5	1.4	2.2	1.4	0.8
Detection rates of breast cancer						
DCIS	1.3	2.0	2.1	2.2	1.7	2.0
Invasive cancer						
pT1mic-a–b	1.0	1.8	3.4	2.3	1.8	4.1
pT1c	1.3	1.9	3.6	2.8	2.3	4.0
pT2–4	0.6	0.9	2.2	1.1	0.9	1.4
pN-negative	2.0	3.3	6.2	4.6	3.6	7.6
pN-positive	0.9	1.2	3.0	1.6	1.4	1.9
Total invasive cancer*	3.0	4.8	9.6	6.7	5.2	10.0
Total breast cancer*	4.3	6.7	11.7	8.9	6.8	12.0

FNA fine-needle aspiration; NCB needle core biopsy; VAB vacuum-assisted biopsy; DCIS ductal carcinoma in situ
 Recall indicates recall for further assessment. Non-invasive assessment indicates one or more among ultrasound, diagnostic mammography, breast physical examination, and other tests without pathologic evaluation. Surgical referral indicates referral for excisional biopsy or definitive surgical treatment. Surgical biopsy indicates excisional biopsy or definitive surgical treatment. Second and subsequent screens indicate the second, third, fourth, and fifth annual screen for women aged 45–49 years, and the second and third biennial screen for women aged 50–54 years and 55–69 years

*Including pTX and pNX invasive cancers and invasive cancers with missing pT and pN information

Table 3 Recall rate, assessment rate by type, surgical referral and surgical biopsy rates, and detection rate of breast cancer at the first screen and homologous cumulative rates at the second and subsequent screens: ratio between women aged 45–49 years and women aged 50–54 years and 55–69 years. Emilia-Romagna Region mammography screening programme (2011–2015)

	Rate ratio (95% CI) at the first screen		Cumulative rate ratio (95% CI) at the second and subsequent screens	
	45–49 vs. 50–54	45–49 vs. 55–69	45–49 vs. 50–54	45–49 vs. 55–69
Recall rate	1.11 (1.07–1.15)	1.11 (1.07–1.16)	2.10 (2.06–2.13)	2.77 (2.73–2.80)
Assessment rates				
Non-invasive assessment	1.19 (1.14–1.24)	1.24 (1.18–1.31)	2.23 (2.20–2.27)	3.32 (3.28–3.37)
Invasive assessment				
FNA	0.86 (0.78–0.93)	1.06 (0.94–1.19)	1.73 (1.65–1.81)	1.59 (1.54–1.64)
NCB, VAB	1.07 (0.96–1.18)	0.82 (0.73–0.92)	1.54 (1.47–1.61)	1.53 (1.48–1.59)
Total invasive assessment	0.94 (0.88–1.01)	0.94 (0.86–1.01)	1.63 (1.58–1.68)	1.56 (1.52–1.60)
Surgical referral rate	0.68 (0.61–0.76)	0.44 (0.39–0.50)	1.32 (1.25–1.39)	0.89 (0.86–0.93)
Surgical biopsy rate	0.68 (0.60–0.76)	0.45 (0.40–0.50)	1.35 (1.28–1.43)	0.88 (0.85–0.92)
Detection rate of benign breast lesion	0.90 (0.69–1.18)	0.98 (0.70–1.38)	1.56 (1.37–1.77)	2.71 (2.42–3.02)
Detection rates of breast cancer				
DCIS	0.66 (0.51–0.84)	0.63 (0.47–0.84)	1.29 (1.14–1.46)	1.07 (0.98–1.17)
Invasive cancer				
pT1mic-a-b	0.57 (0.44–0.74)	0.30 (0.23–0.38)	1.26 (1.12–1.42)	0.56 (0.52–0.61)
pT1c	0.69 (0.53–0.88)	0.35 (0.28–0.45)	1.24 (1.12–1.38)	0.70 (0.65–0.75)
pT2–4	0.61 (0.42–0.87)	0.25 (0.18–0.35)	1.29 (1.09–1.54)	0.79 (0.70–0.89)
pN-negative	0.60 (0.49–0.73)	0.32 (0.27–0.39)	1.27 (1.17–1.39)	0.61 (0.57–0.64)
pN-positive	0.75 (0.55–1.03)	0.30 (0.23–0.39)	1.16 (1.01–1.33)	0.85 (0.77–0.94)
Total invasive cancers*	0.63 (0.53–0.73)	0.31 (0.27–0.36)	1.30 (1.21–1.39)	0.67 (0.64–0.70)
Total breast cancers*	0.63 (0.55–0.72)	0.37 (0.32–0.42)	1.30 (1.22–1.38)	0.74 (0.71–0.77)

FNA fine-needle aspiration; NCB needle core biopsy; VAB vacuum-assisted biopsy; DCIS ductal carcinoma in situ; CI confidence interval

All ratios are based on data in Table 2

Recall indicates recall for further assessment. Non-invasive assessment indicates one or more among ultrasound, diagnostic mammography, breast physical examination, and other tests without pathologic evaluation. Surgical referral indicates referral for excisional biopsy or definitive surgical treatment. Surgical biopsy indicates excisional biopsy or definitive surgical treatment. Second and subsequent screens indicate the second, third, fourth and fifth annual screen for women aged 45–49 years, and the second and third biennial screen for women aged 50–54 years and 55–69 years

*Including pTX and pNX invasive cancers and invasive cancers with missing pT and pN information

than among older women. Similarly, an excess prevalence of DCIS was observed only when comparing younger women with women aged 50–54 years.

The 5-year cumulative rates are shown in the Electronic Supplementary Material Table S1. Their ratios are shown in the Electronic Supplementary Material Table S2.

DCIS to invasive cancer ratio, tumour stage, PPV, and patterns of treatment

These indicators are shown in Table 4 and are compared in Table 5. Whether at the first or subsequent screens, the DCIS to invasive cancer ratio did not differ significantly between women aged 45–49 years and the intermediate age group. A significant excess of DCIS was observed when comparing younger women with women aged 55 years or older, with a

ratio of 2.02 at the first screen and 1.60 at the second and subsequent screens.

Both the pT and pN distribution of invasive cancers showed only modest and nonsignificant differences between age groups, except for a 27% excess prevalence of pN-positive cancers among younger women at the second and subsequent screens compared with those aged 55–69 years.

The PPVs showed the same pattern at all screens. For younger women, the PPVs of mammography for DCIS and invasive cancer were much lower than in the other two age groups, with ratios of 0.56 and 0.32 at the first screen and 0.62 and 0.27 at the second and subsequent screens. For the PPV of surgical biopsy, the figures were substantially higher, i.e. 0.93 and 0.82 and, respectively, 0.96 and 0.83.

Finally, the proportion of invasive cancers undergoing breast-conserving surgery was similar across the age groups both at the first screen and at the subsequent ones.

Table 4 DCIS to invasive cancer ratio, pT and pN distribution, positive predictive value of mammography, surgical referral and surgical biopsy, and proportion of cancers undergoing breast-conserving surgery at the first screen and at the second and subsequent screens, by woman's age

group. Except for the DCIS to invasive cancer ratio, all values are percentages. Emilia-Romagna Region mammography screening programme (2011–2015)

	Value at the first screen			Value at the second and subsequent screens		
	45–49	50–54	55–69	45–49	50–54	55–69
DCIS to invasive cancer ratio	0.43	0.41	0.21	0.32	0.32	0.20
pT1mic-a–b/total invasive cancer	33.5	36.9	34.9	34.1	35.0	40.5
pT1c/total invasive cancer	42.5	38.8	37.2	42.2	44.0	40.3
pT2–4/total invasive cancer	18.6	19.2	22.9	16.8	16.8	14.2
pN-negative/total invasive cancer	66.3	69.2	64.0	69.0	70.4	75.9
pN-positive/total invasive cancer	29.3	24.3	30.6	23.7	26.5	18.6
Positive predictive value						
Of mammography, for invasive cancer*	2.9	5.3	11.0	3.2	5.2	13.5
Of mammography, for DCIS and invasive cancer*	4.2	7.4	13.3	4.3	6.9	16.2
Of surgical referral, for invasive cancer*	47.8	52.2	68.4	54.7	55.6	73.1
Of surgical referral, for DCIS and invasive cancer*	68.5	73.7	83.0	72.4	73.7	87.9
Of surgical biopsy, for invasive cancer*	50.9	55.3	73.3	58.3	60.7	77.1
Of surgical biopsy, for DCIS and invasive cancer*	72.8	78.0	88.9	77.2	80.5	92.7
Treated with breast-conserving surgery/pT1	79.4	84.0	90.9	85.7	85.8	91.7
Treated with breast-conserving surgery/total treated [†]	72.7	78.8	80.1	78.8	81.1	85.7

DCIS ductal carcinoma in situ

Surgical referral indicates referral for excisional biopsy or definitive surgical treatment. Surgical biopsy indicates excisional biopsy or definitive surgical treatment. Second and subsequent screens indicate the second, third, fourth, and fifth annual screen for women aged 45–49 years, and the second and third biennial screen for women aged 50–54 years and 55–69 years

*Including pTX and pNX invasive cancers and invasive cancers with missing pT and pN information

[†] Pooling DCIS cases and invasive cancers

Additional data

The proportion of screen-detected cancers with preoperative cytological and histological diagnoses was determined for a total of 920 women. For women aged 45–49 years, 50–54 years, and 55–69 years, the preoperative diagnosis rate was 79.1%, 80.4%, and 86.6%, respectively. The ratio for younger women vs. the two groups of older ones was 0.98 (95% CI, 0.89–1.09) and 0.91 (95% CI, 0.85–0.99).

Discussion

Open questions

The age at which to start inviting women to mammography continues to be an area of debate. For most experts, the decision to invite women under 50 years of age should be based on whether the benefits (reduced breast cancer mortality, less intensive or mutilating treatments, and improved quality of life) outweigh the associated harms and risks (radiation exposure, false-positive and false-negative screening results, and occurrence of overdiagnosis) [20–22].

The balance between these factors, however, is uncertain for several reasons. In particular, randomised controlled trials do not provide a strong basis for determining the effectiveness of mammography in younger women [23], the evidence for an impact on the risk of advanced disease is of low quality [6], and the methods of estimate of overdiagnosis are disputed [24]. Another opinion is that additional factors need to be considered, including the evidences from observational studies [6], the detection rate of breast cancer by age [25], and the level of cost-effectiveness [20, 26]. The uncertainties explain why the recommended age at which to begin screening varies between medical agencies and organisations from 40 years [27] to 45 years [6, 7] to 50 years [2, 3].

The debate on the baseline age for screening is interrelated with the debate on the screening interval. According to the U.S. Preventive Services Task Force, biennial mammography screening provides the best balance of benefit and harms for most women, including younger ones [3]. According to the International Agency for the Research on Cancer and the ECIBC Guideline Development Group, conversely, the available data do not allow for the establishment of the most appropriate interval [2, 6].

Table 5 DCIS to invasive cancer ratio, pT and pN distribution, positive predictive value of mammography, surgical referral and surgical biopsy, and proportion of cancers undergoing breast-conserving surgery at the first screen and at the second and subsequent screens: ratio between

women aged 45–49 years and women aged 50–54 years and 55–69 years. Emilia-Romagna Region mammography screening programme (2011–2015)

	Ratio (95% CI) at the first screen		Ratio (95% CI) at the second and subsequent screens	
	45–49 vs. 50–54	45–49 vs. 55–69	45–49 vs. 50–54	45–49 vs. 55–69
DCIS to invasive cancer ratio	1.05 (0.77–1.42)	2.02 (1.44–2.87)	1.00 (0.78–1.26)	1.60 (1.32–1.94)
pT1mic-a-b/total invasive cancer	0.91 (0.73–1.12)	0.96 (0.78–1.18)	0.97 (0.83–1.14)	0.84 (0.75–0.95)
pT1c/total invasive cancer	1.10 (0.90–1.33)	1.14 (0.95–1.38)	0.96 (0.84–1.09)	1.05 (0.94–1.16)
pT2–4/total invasive cancer	0.97 (0.70–1.35)	0.81 (0.61–1.08)	1.00 (0.77–1.29)	1.18 (0.97–1.44)
pN-negative/total invasive cancer	0.96 (0.86–1.07)	1.04 (0.93–1.16)	0.98 (0.91–1.06)	0.91 (0.86–0.96)
pN-positive/total invasive cancer	1.21 (0.92–1.58)	0.96 (0.76–1.20)	0.89 (0.73–1.09)	1.27 (1.08–1.50)
Positive predictive value				
of mammography, for invasive cancer*	0.56 (0.48–0.65)	0.27 (0.23–0.31)	0.62 (0.55–0.69)	0.24 (0.22–0.26)
of mammography, for DCIS and invasive cancer*	0.56 (0.50–0.64)	0.32 (0.28–0.36)	0.62 (0.56–0.68)	0.27 (0.25–0.29)
of surgical referral, for invasive cancer*	0.92 (0.82–1.02)	0.70 (0.64–0.77)	0.98 (0.91–1.06)	0.75 (0.71–0.79)
of surgical referral, for DCIS and invasive cancer*	0.93 (0.87–1.00)	0.82 (0.78–0.88)	0.98 (0.93–1.03)	0.82 (0.79–0.86)
of surgical biopsy, for invasive cancer*	0.92 (0.83–1.02)	0.69 (0.64–0.76)	0.96 (0.89–1.03)	0.76 (0.71–0.80)
of surgical biopsy, for DCIS and invasive cancer*	0.93 (0.87–0.99)	0.82 (0.78–0.86)	0.96 (0.92–1.00)	0.83 (0.80–0.86)
Treated with breast-conserving surgery/pT1	0.95 (0.87–1.03)	0.87 (0.80–0.95)	1.00 (0.95–1.05)	0.93 (0.89–0.98)
Treated with breast-conserving surgery/total treated†	0.92 (0.85–1.01)	0.91 (0.82–1.01)	0.97 (0.92–1.03)	0.92 (0.87–0.97)

DCIS ductal carcinoma in situ; CI confidence interval

All ratios are based on data in Table 4

Surgical referral indicates referral for excisional biopsy or definitive surgical treatment. Surgical biopsy indicates excisional biopsy or definitive surgical treatment. Second and subsequent screens indicate the second, third, fourth and fifth annual screen for women aged 45–49 years, and the second and third biennial screen for women aged 50–54 years and 55–69 years

*Including pTX and pNX invasive cancers and invasive cancers with missing pT and pN information

† Pooling DCIS cases and invasive cancers

Comments to main results

It is commonly supposed that an increased frequency of recalls, surgical referrals, and surgical biopsies is an unavoidable consequence of screening women aged 40–49 years [9, 20, 28]. If so, this would unfavourably affect the feasibility of the process. As the prevalence of cancer decreases with decreasing age, a rise in recall and surgical referral and biopsy rates would cause the PPV of mammography and surgical indication to be poorer among younger women.

Our results confirm only in part these assumptions. In a population of women aged 45–49 years undergoing annual screening, we actually found a two- to threefold higher cumulative recall rate at the second and subsequent screens. With respect to surgical referrals and biopsies, conversely, they had lower rates at the first screen. At the second and subsequent screens, they had only moderately higher rates and only if compared with women aged 50–54 years.

This is explained by the fact that, over recent years, the increasing use of percutaneous sampling techniques has greatly improved the specificity of the diagnostic work-up

of screen-detected abnormalities. When the PPV of surgical referral and surgical biopsy approaches 100%, a poorer prevalence of disease (which is the case for women aged 45–49 years compared with the third age group) automatically translates into a lower rate of unnecessary referrals and biopsies [29].

Two more points should be made. At the first screen, the invasive assessment rate was the same for younger women as for the two groups of older ones. At the second and subsequent screens, younger women experienced a much larger increase in non-invasive than in invasive assessment rate. It appears that the mammographic abnormalities detected in this population generated a lower level of clinical suspicion at assessment.

The second issue to be noted is that younger women benefited from a larger increase in the PPV of surgical biopsy vs. that of mammography. For them, the PPV of mammography for DCIS and invasive cancer was much lower than for women aged 50–54 and 55–69 years both at the first screen and thereafter, whereas the PPV of surgical biopsy was only slightly less. This indicates that percutaneous sampling

techniques have a particularly favourable impact on younger women.

The objective of short-interval rescreen is to balance the poorer sensitivity of mammography that is due to the greater breast density and the more rapid tumour growth [30]. In fact, an increased breast density explains most of the excess odds of women aged 40–49 years having an interval cancer in the first interval year, whereas a rapid tumour growth contributes mostly to the excess odds in the second year [31]. Consequently, a 12-month screening interval is expected to reduce, in particular, the adverse impact of fast-growing tumours. Our results are compatible with this rationale, since the percentage of large-sized tumours was very similar to that found in older women undergoing biennial screening.

By implication, our data provide only limited support to the recommendation for annual screening of women aged 50–54 years [7]. In comparative terms, their tumour stage distribution was not adversely affected by the 24-month interval. Previous studies have already suggested that women between 45 and 54 years of age are not a mammographically homogeneous population. While women under 50 years of age undergoing biennial screening are more likely to have late-stage disease at diagnosis than those screened annually, this is not the case for women aged ≥ 50 years [32–34].

Policy implications

The set of performance measures that we considered in this study—from the recall rates to the detection rates—determines the demands that an annual screening programme places on breast care services. According to our results, screening younger women requires a relatively higher level of investment in outpatient diagnostic work-up services than in inpatient surgical services. If the decision to offer annual mammography to women aged 45–49 years is taken, screening providers should primarily expect a high cumulative burden of recalls. The adverse effects of the low age of women on the frequency and PPV of surgical referral and biopsy are of relatively lesser magnitude. These findings may be useful in designing simulation model studies to evaluate the cost-effectiveness of annual screening in this population [26].

Strengths and weaknesses

There are many strengths in this study, namely: its considerable statistical power; its large multicentre basis, which allows for the results to be safely generalised to other settings; and its high degree of novelty. To our knowledge, no previous comparable data have been published.

The major weakness of the study is that the incidence of interval breast cancer and the cumulative incidence of advanced breast cancer using a cohort design remain to be assessed. At the time we are writing this article, a substantial

part of negative mammography results of 2011–2015 cannot yet be followed up due to the latency time of cancer registration. In addition, estimating overdiagnosis is quite premature [35].

Another limitation of the study is that the data were collected in an aggregate form. As a consequence, we were unable to evaluate their consistency in a direct manner. However, as they were taken from national surveys conducted by two specialised bodies, we assume that their quality was acceptable [13, 14].

Conclusions

In summary, compared with 5 years of biennial screening in the age range 50–54 and 55–69, 5 years of annual screening between age 45 and 49 were associated with two- to threefold higher cumulative recall rates at second and subsequent screens, and with much more limited differences in the frequency and PPV of surgical referral and biopsy and in the detection rate of breast cancer. The high specificity of current assessment techniques for screen-detected abnormalities had a greater impact on younger women. Albeit encouraging, these results must be completed with further investigation, especially on interval cancer incidence.

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Methodology

- retrospective
- observational
- multicentre study

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