

Impact of different age ranges on the benefits and harms of the breast cancer screening programme by the EU-TOPIA tool

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Background: The recommendation for the implementation of mammography screening in women aged 45–49 and 70–74 is conditional with moderate certainty of the evidence. The aim of this study is to simulate the long-term outcomes (2020–50) of using different age range scenarios in the breast cancer screening programme of the Valencia Region (Spain), considering different programme participation rates. **Methods:** Three age range scenarios (S) were simulated with the EU-TOPIA tool, considering a biennial screening interval: S1, 45–69 years old (y); S2, 50–69 y and S3, 45–74 y. Simulations were performed for four participation rates: A = current participation (72.7%), B = +5%, C = +10% and D = +20%. Considered benefits: number (N°) of *in situ* and invasive breast cancers (BC) (screen vs. clinically detected), N° of BC deaths and % BC mortality reduction. Considered harms: N° of false positives (FP) and % overdiagnosis. **Results:** The results showed that BC mortality decreased in all scenarios, being higher in S3_A (32.2%) than S1_A (30.6%) and S2_A (27.9%). Harms decreased in S2_A vs. S1_A (N° FP: 236 vs. 423, overdiagnosis: 4.9% vs. 5.0%) but also benefits (BC mortality reduction: 27.9% vs. 30.6%, N° screen-detected invasive BC 15/28 vs. 18/25). In S3_A vs. S1_A, an increase in benefits was observed (BC mortality reduction: 32.2% vs. 30.6%), N° screen-detected *in situ* B: 5/2 vs. 4/3, but also in harms (N° FP: 460 vs. 423, overdiagnosis: 5.8% vs. 5.0%). Similar trends were observed with increased participation. **Conclusions:** As the age range increases, so does not only the reduction in BC mortality, but also the probability of FP and overdiagnosis.

Introduction

In 2020, there were 2 million new cases of breast cancer (BC) and 600 thousand deaths were caused by this disease worldwide.¹ In Spain, it is the second most common type of tumour in women and the second leading cause of cancer deaths in this population group.² Due to the high incidence and mortality of BC, it is a significant public health problem and international organizations are joining forces to prevent the burden of this disease and ensure that it is diagnosed at an early stage.

Breast cancer screening programmes (BCSP) are the main strategy implemented to facilitate the early diagnosis of cancer. BCSP vary between European countries due to differences in the organization of healthcare services and the available resources.³ The BCSP of the Valencia Region (BCSP-VR) in Spain was established in 1992. This organized programme targets asymptomatic women aged between 45 and 69 who are invited to take part in biennial mammography screening.⁴

BCSP are aimed at a large asymptomatic population and must therefore ensure that the benefits and harms are appropriately balanced, in accordance with the recommendation of European Guidelines.⁵ One of the main long-term benefits is a reduction in BC mortality due to an increase in the number of early-stage BC diagnosed in screening.⁵

Overdiagnosis and false positives are the most common harms associated with BCSP. Overdiagnosis is one of the main harm, defined as the diagnosis of an asymptomatic tumour that would never have been detected without screening. On the other hand, false positives are lesions that are histologically confirmed to be benign following a positive screening test.⁵

The BCSP participation rate, which is the number of women who undergo the screening test as a proportion of the total number of women invited,⁵ is a key aspect in the quality of screening. In order to achieve the expected benefits, European recommendations establish an acceptable participation level of >70% or a desired level of ≥75% for BCSP.⁵ The BCSP-VR has a participation rate of 72.7%

and therefore meets the acceptable targets established by European recommendations.

The European Commission Initiative on Breast Cancer⁶ supports biennial mammography screening in the context of an organized screening programme for women aged between 50 and 69 as a strong recommendation with moderate certainty of the evidence. According to this guideline, this is the most suitable and cost-effective scenario. Mammography screening is not recommended in women aged 40–44, while the recommendation is conditional with moderate evidence in women aged 45–49 and 70–74.

In the case of women aged 40–49, some studies observe an increase in benefits when this population group is included, namely a decrease in mortality and the number of advanced cancers.^{7,8} Schünemann *et al.*⁹ demonstrate that these benefits are seen to a greater degree in women aged 45–49 than in women aged 40–44. However, an increase in the number of false positives was also observed in women aged 40–49, but to a lesser extent in women aged under 44.⁹ Nonetheless, not all studies observe this trend.⁷

It has also been observed that including women aged 70–74 in BCSP entails a decrease in mortality and the number of advanced cancers.^{9,10} However, an increase in overdiagnosis and false positives was also observed in this age group.¹¹

To be able to assess the impact of different age groups on breast cancer screening, the aim of this study is to simulate the long-term outcomes of different age range scenarios in the BCSP-VR considering different programme participation rates.

Methods

Study design

This is a long-term impact simulation study (2020–50) of three screening scenarios considering different programme participation rates. The study area is the Valencia Region (Spain).

The EU-TOPIA evaluation tool

The EU-TOPIA evaluation tool was used to perform this study. The aim of this tool is to estimate the impact of possible changes in a BCSP, such as the target population, the screening interval or the participation rate on benefits and harms.¹²

The EU-TOPIA evaluation tool (<https://miscan.eu-topia.org>), developed as part of the European EU-TOPIA project (<https://eu-topia.org/>), is based on the Microsimulation Screening Analysis (MISCAN) model.^{13,14} This model allows simulating individual life events with and without breast cancer and in the presence or absence of screening or treatment, taking into account the natural history of the disease. Simulated life events include birth, the onset of a pre-clinical ductal carcinoma *in situ* (DCIS), transitions between disease states, participation in screening, and the onset of screen-detected or clinical detected cancers.³

Data and information sources

In order to obtain long-term estimates that reflect the characteristics and situation of each country, the tool uses demographic and epidemiological information (BC incidence and mortality by age group in two periods [1981–85 and 2010–15], survival by stage, and an estimation of the population size in 2018–50 by age group), as well as screening information (size of the target population, invited and screened population as a proportion of the total population and by screening history [initial screening, successive screening], screening outcomes, additional assessments, final result, lesion type, treatment type and interval cancers). These data are collected and uploaded to the tool in an Excel Data Template.

For this study, demographic and epidemiological information on women from the Valencia Region (VR) between 2010 and 2015 was collected from the Spanish National Statistics Institute¹⁵ and the Valencia Region's Oncological Information System. Screening

information was obtained from BCSP-VR records relative to 2016, which, in turn, are taken from the programme's specific information system. In 2016, the overall participation was 72.7%, distributed between the different age groups as follows: 67.9% in women aged 45–49, 72.0% in women aged 50–54, 73.9% in women aged 55–59, 76.6% in women aged 60–64 and 75.8% in women aged 65–69.

This study was approved by the Research Ethics Committee of the General Directorate of Public Health and the Advanced Public Health Research Centre (CEI DGSP-CSISP) on 26 November 2020 (reference: 20201126/07).

Screening scenarios

We simulated three scenarios (S). S1 represents the current target population of the BCSP-VR (women aged 45–69). S2 simulates the results for women aged 50–69, which implies excluding women aged 45–49. Finally, S3 simulates the results for women aged 45–74, which implies including women aged 70–74. Each of these scenarios was simulated for four different BCSP-VR participation situations: A = current participation (from 2016), B = A + 5%, C = A + 10% and D = A + 20% (A = 72.7%; B = 77.7%; C = 82.7%; D = 92.7%).

Impact indicators

Impact indicators for the 2020–50 period were estimated in women aged between 40 and 100 for each S. Firstly, incidence and mortality for each year of the study period were estimated. Subsequently, the number (N°) of screening mammograms and the N° of additional assessments were estimated. The following screening benefits were estimated: N° of screen-detected *in situ* and invasive BC vs. N° of clinically detected cases, N° of deaths due to BC and % reduction in BC mortality. The harms were the N° of FP and the % overdiagnosis. Further synthetic indices were also estimated, such as the N° of screening tests per prevented death and the N° of false positives per prevented death.

The results of the S with different participation situations were compared, and S1 (women aged 45–59) with the current participation rate (A) from 2016 was taken as the baseline.

Results

The estimated population aged between 40 and 100 was 1,487 000 in 2020.

Raw breast cancer mortality and incidence

Figure 1 shows the raw incidence of BC in the VR, estimated for each year from 2020–50 in accordance with the three simulated screening scenarios. Differences in the BC incidence trend are observed among the scenarios, with S2 showing an increase between 2020 and 2025 and S3 a marked decrease during this same time period. From 2025 onwards, the incidence shows a similar trend across all scenarios, estimated at a rate of 100–110 (per 100 000 women per year). In addition, a slightly higher incidence can be observed in S3 than in S1 and S2.

Figure 2 describes the estimated BC mortality rate and shows that the rates among scenarios are similar (25–30 per 100 000 women per year) between 2020 and 2025. From 2025 onwards, there are some differences between scenarios but all of them show a notable decrease in mortality rates, with S3 showing the higher decrease for all participation situations.

Benefits and harms

Table 1 contains the results of the overall impact estimations for the three scenarios during the 2020–50 period, based on the different participation situations.

For the current participation rate (A) from 2016 (table 1), the screening burden increases as the age range widens, and S3 requires

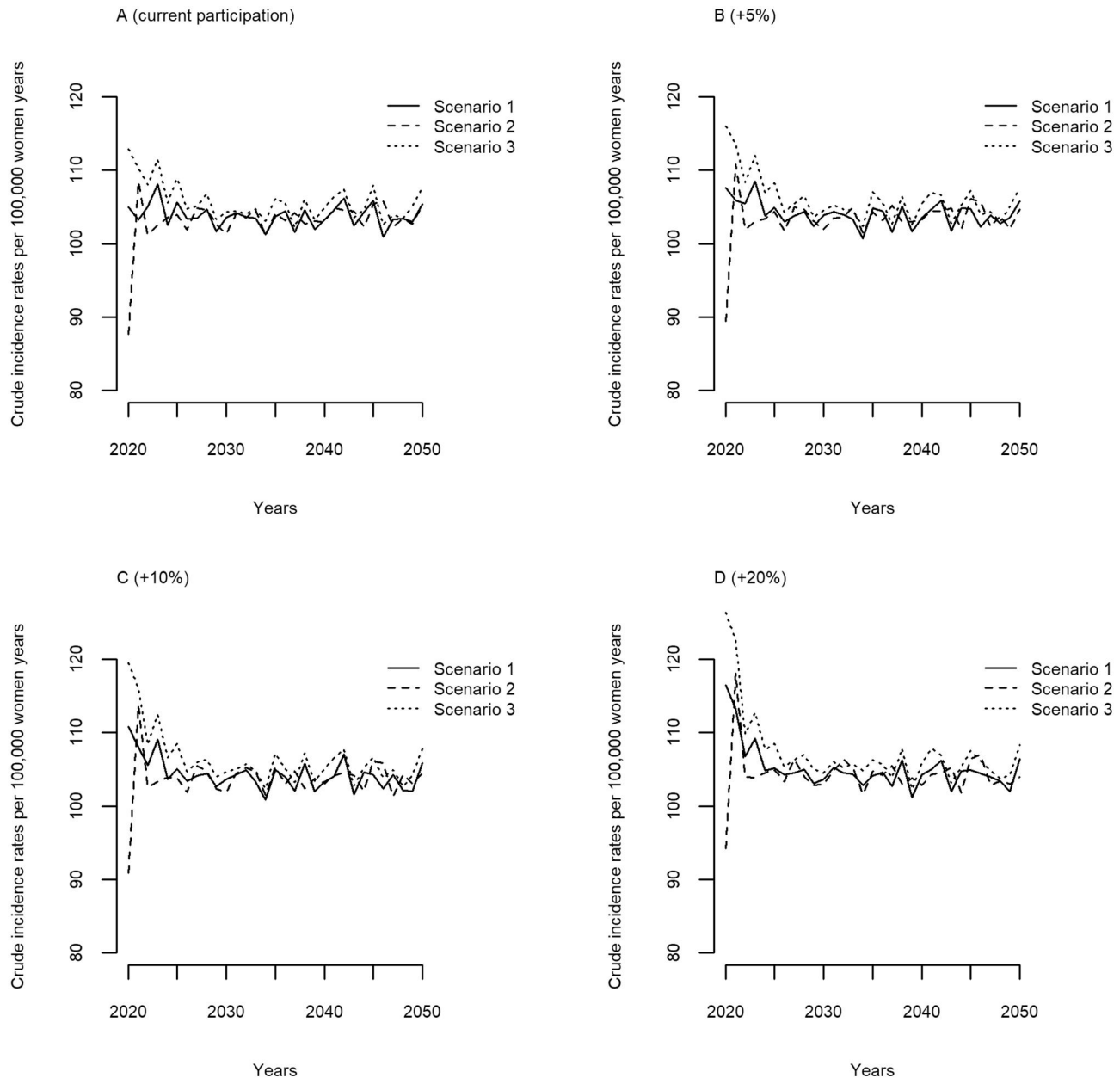


Figure 1 BC incidence on the current and increased participation for the three simulated scenarios. A, current participation from 2016; B=+5% participation, C=+10% participation. D=+20% participation. Scenario 1: women aged 45–69, Scenario 2: women aged 50–69 and Scenario 3: women aged 45–74.

the highest N° of screening mammograms ($n = 10\,858$) and additional assessments ($n = 485$) in the study period. As regards benefit indicators, S3 provides the best ratio of screen-detected to clinically detected *in situ* BCs (5/2), as compared with S1 and S2 (4/3 in both cases). Furthermore, this scenario achieves the highest % reduction in mortality (32.2% in S3 vs. 30.6% in S1 and 27.9% in S2). In contrast, S3 presents the worst results in terms of harms, with an increase in the N° of false positives (S3 = 460, S1 = 423 and S2 = 236) and % overdiagnosis (S3 = 5.8%, S1 = 5.0% and S2 = 4.9%). A reduction of FP can be seen in S2 as compared with S1 (S2 = 236 vs. S1 = 423), in addition to a decrease in the % BC overdiagnosis (S2 = 4.9% vs. S1 = 5.0%).

The results for situations with increased participation rates (B, C, and D) showed the same trend as the S simulated with the current participation rate (A) (table 1). As the participation rate increases, so does the % reduction in mortality in all of the simulated age range scenarios (S1: B = 31.2%, C = 32.0% and D = 33.4%; S2: B = 28.6%, C = 29.1% and D = 30.3% and S3: B = 32.9%, C = 33.7% and

D = 35.2%). However, an increase is also observed in the N° of FP (S1: B = 455, C = 487, D = 552; S2: B = 254, C = 272 and D = 308; and S3: B = 495, C = 530 and D = 600).

Finally, we observe a greater screening burden per prevented death for scenarios with a wider age range in the synthetic indices. The number of FP per prevented death follows the same trend (table 1).

Discussion

This study shows that larger screening age ranges and higher participation rates could be associated with greater benefits, but also with greater harms. Nevertheless, extending age ranges might have a larger impact than increasing participation.

The scenario including women aged 45–74 (S3) provides the greatest benefits and harms, as observed in other studies.¹⁴ An increase in the number of screen-detected *in situ* cancers and a higher % reduction in BC mortality can be seen in this scenario as

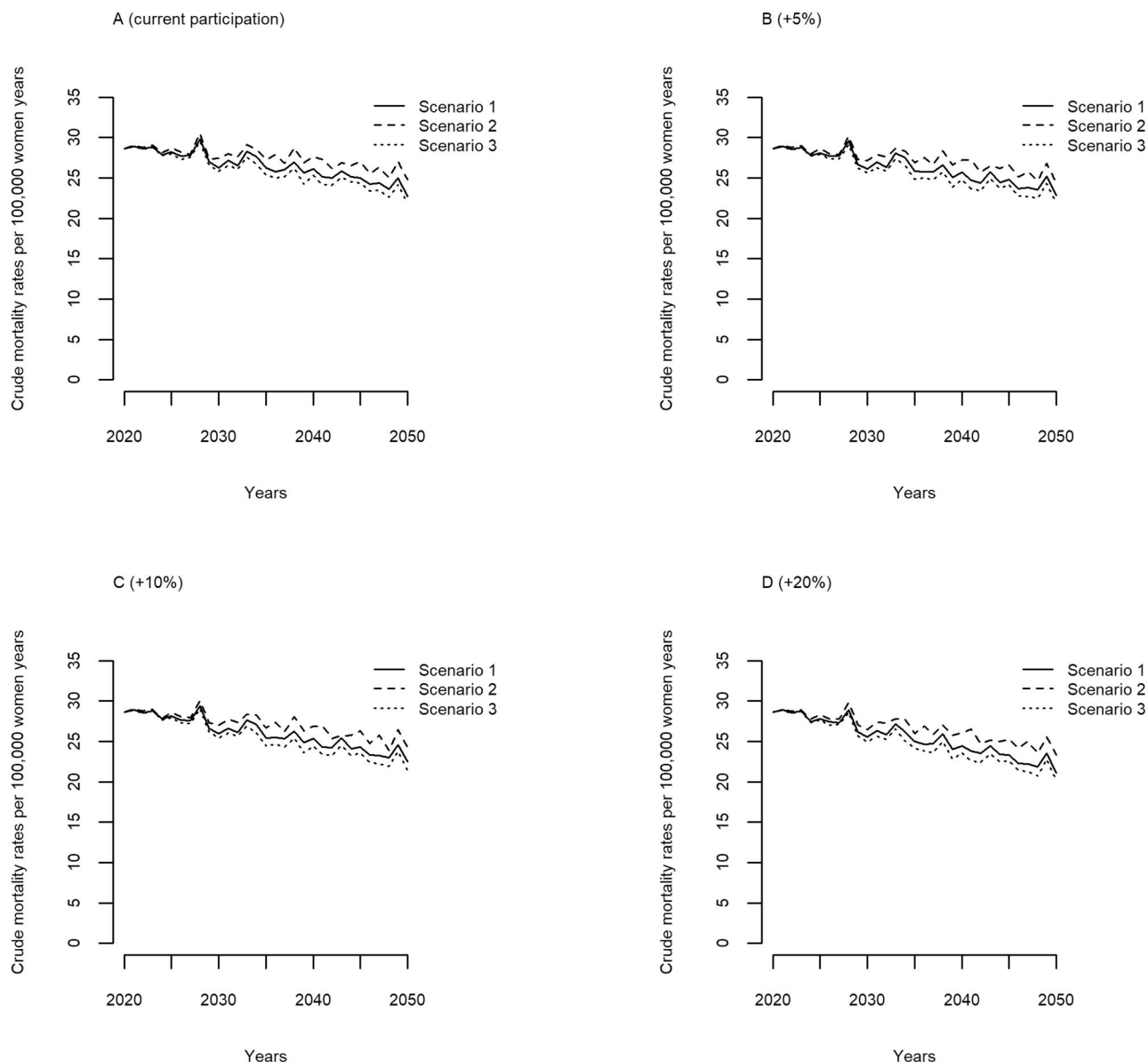


Figure 2 BC mortality on the current and increased participation for the three simulated scenarios. A=current participation from 2016, B=+5% participation, C=+10% participation and D=+20% participation. Scenario 1: women aged 45–69. Scenario 2: women aged 50–69. Scenario 3: women aged 45–74.

Table 1 Impact estimation of three scenarios on the BCSP-VR with current and increased participation ($\times 1000$)

	S1. 45–69y				S2. 50–69y				S3. 45–74y			
	A	B	C	D	A	B	C	D	A	B	C	D
Screening load												
No. of screen tests ($\times 1000$)	9641	10 357	11 073	12 503	7661	8227	8793	9924	10 858	11 664	12 470	14 081
No. of referrals ($\times 1000$)	445	478	511	578	255	274	282	330	485	521	558	630
Benefits												
No. of BC <i>in situ</i> (screen/clinically detected) ($\times 1000$)	4/3	5/3	5/3	5/2	4/3	4/3	4/3	4/3	5/2	5/2	5/2	6/2
No. of BC invasive (screen/clinically detected) ($\times 1000$)	18/25	18/25	19/24	20/23	15/28	16/27	16/27	18/25	21/23	21/22	22/21	24/20
No. of BC deaths ($\times 1000$)	13	13	13	12	13	13	13	13	12	12	12	12
BC mortality reduction (%)	30.6	31.2	32.0	33.4	27.9	28.6	29.1	30.3	32.2	32.9	33.7	35.2
Harms												
No. of false positives ($\times 1000$)	423	455	487	552	236	254	272	308	460	495	530	600
Overdiagnosis (% of screen detected)	5.0	5.0	4.9	5.0	4.9	4.9	4.9	4.9	4.8	5.8	5.8	5.8
Synthetic indices												
No. of screening tests per BC death Prevented ($\times 1000$)	1709	1801	1882	2032	1490	1564	1640	1777	1830	1926	2012	2172
No. of false positives per BC death prevented ($\times 1000$)	75	79	83	90	46	48	51	55	77	82	86	93

Note: A=current participation from 2016, B=+5% participation, C=+10% participation and D=+20% participation.

compared with S1 and S2. On the one hand, this could be caused by an increase in the number of people taking part in screening as this scenario has the largest age range. On the other hand, as it includes women aged over 70, it may detect cancers in more advanced stages and thereby improve survival in this age group.^{9,10} However, this scenario also generates more harms, with the largest number of FP and highest % overdiagnosis, in line with other studies.¹³ The increased number of FP could be explained by the fact that the scenario includes women aged 45–49, who typically have a higher mammographic density,¹⁶ which hinders the sensitivity and specificity of the screening test.¹⁷ In addition, the high % overdiagnosis could be due to the inclusion of women aged 70–74, as there is a high probability of detecting asymptomatic tumours that would not have limited life expectancy in this group.^{11,18}

The scenario that includes women aged 50–69 shows a reduction in the harms of screening, namely a decrease in the number of FP and the % overdiagnosis, but also in the benefits, especially in terms of BC mortality reduction. This scenario is currently recommended by European guidelines.^{5,6} The reduction in the number of FP could be due to the fact that the scenario excludes women aged 45–49, who have the highest risk of receiving a FP in the screening test.¹⁶ In addition, the smaller age range could also explain the lower % reduction in BC mortality.

The BCSP-VR, which targets women aged 45–69, had a participation rate of 72.7% in 2016. The estimations of the present study were calculated using this participation rate, which is above the acceptable value recommended by the European Commission.⁵ Scenarios were simulated with gradual increments of 5%, 10% and 20%. A progressive and slight increase of the main benefit (BC mortality reduction), but also of harms, can be seen in each of these situations. These slight differences between scenarios may be due to the high baseline participation rate of the BCSP-VR, which indicates the importance of achieving the participation rates recommended by the European Commission.⁵

Considering the European Commission's current recommendation to expand screening age ranges to women aged 45–49 and 70–74 with a low certainty of evidence,⁶ which is partly due to the scarce number of publications on this topic, the results of this study help increase knowledge regarding the effect of including these groups on the BCSP.

One limitation of our study is that the three simulated scenarios consider a biennial screening test, and we could not contemplate different screening intervals due to usage limitations of the EU-TOPIA evaluation tool. A recent systematic review observed that annual, biennial, and triennial screening tests could have a different impact on benefits and harms depending on the age group.¹⁹ A less favourable balance could be observed for women aged 45–49 with annual screening, while a more favourable balance could be seen for women aged 70–74 with triennial screening.¹⁹ Therefore, continuing investigation is required in this regard.

Although our results are based on mathematical estimations using real data, we must appreciate the enormous potential and usability of the EU-TOPIA evaluation tool. MISCAN is an internationally validated model to predict the efficacy of BC screening.¹² Furthermore, the development of the web-based tool makes it easier for screening programme coordinators and managers to use the EU-TOPIA evaluation tool, thereby helping generate evidence that can aid decision-making.

Given that this study shows that both benefits and harms increase with age ranges and participation rates, decision-making is complex. In any case, these results can be used in evidence-based decision-making to improve the organization of population-based BCSP in Spain and in other contexts with similar characteristics to the BCSP-VR. Nonetheless, complementary studies analysing the cost-effectiveness of each screening scenario are required, as well as analyses of different screening intervals for the various age groups.

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Conflict of interest

The authors declare that they have no competing interests.

Data availability

The demographic data used to perform this study are available on the Spanish National Statistics Institute website (<https://www.ine.es/>). The data from the Breast Cancer Screening Programme of Valencia Region used for this study are not publicly available due to legal restrictions on sharing the dataset, as regulated by the Regional Government of Valencia by means of legal resolution from the Valencia Health Agency (2009/13312), which forbids the dissemination of data to third parties (available on: <https://www.san.gva.es/ca/web/investigacio/programas-normativa-y-legislacion>). But, they are available from the Management Office of the Data Commission in the Valencia Health Agency (<https://www.san.gva.es/ca/web/investigacio/acceso-a-la-aplicacion>) on reasonable request.

Key points

- Larger age ranges and participation rates yields greater benefits and harms.
- Increasing participation leads to a gradual decrease in mortality.
- False positives rise in larger age ranges, mainly by including 45–49 group.
- EU-TOPIA tool help evidence-based decision-making in cancer screening programmes.

References

- 1 Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
- 2 ECIS—European Cancer Information System. Available at: <https://ecis.jrc.ec.europa.eu/> (10 February 2022, date last accessed).
- 3 Deandra S, Molina-Barceló A, Uluturk A, et al. Presence, characteristics and equity of access to breast cancer screening programmes in 27 European countries in 2010 and 2014. Results from an international survey. *Prev Med* 2016;91:250–63.
- 4 Informe Anual 2017–2018 N°156. Informes de Salud. Programa de Prevención de Cáncer de Mama. Conselleria de Sanitat Universal i Salut Pública, Generalitat Valenciana. Comunitat Valenciana. 2020. Available at: http://www.sp.san.gva.es/DgspPortal/docs/PPCM_2017_8_cas.pdf (29 March 2024, date last accessed)
- 5 European Commission, Directorate-General for Health and Consumers, Karsa, L, Holland, R, Broeders, M, et al. *European Guidelines for Quality Assurance in Breast Cancer Screening and Overdiagnosis*, 4th edn supplements. Publications Office of the European Union, 2006.
- 6 Janusch-Roi A, Neamtii L, Dimitrova N, et al. *European Commission Initiative on Breast Cancer—Manual for Breast Cancer Services—European Quality Assurance Scheme for Breast Cancer Services*. Luxembourg: Publications Office of the European Union, 2021.
- 7 Duffy SW, Vulkan D, Cuckle H, et al. Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. *Lancet Oncol* 2020;21:1165–72.
- 8 Moss SM, Wale C, Smith R, et al. Effect of mammographic screening from age 40 years on breast cancer mortality in the UK Age trial at 17 years' follow-up: a randomised controlled trial. *Lancet Oncol* 2015;16:1123–32.

- 9 Schünemann HJ, Lerda D, Quinn C, et al.; European Commission Initiative on Breast Cancer (ECIBC) Contributor Group. Breast cancer screening and diagnosis: a synopsis of the European Breast Guidelines. *Ann Intern Med* 2020; 172:46–56.
- 10 Seely JM, Alhassan T. Screening for breast cancer in 2018—What should we be doing today? *Curr Oncol* 2018;25:S115–24.
- 11 Nickson C, Mason KE, Kavanagh AM. Breast cancer screening of women aged 70–74 years: results from a natural experiment across Australia. *Breast Cancer Res Treat* 2014;143:367–72.
- 12 Habbema JD, van Oortmarssen GJ, Lubbe JT, van der Maas PJ. The MISCAN simulation program for the evaluation of screening for disease. *Comput Methods Programs Biomed* 1985;20:79–93.
- 13 Kregting LM, Sankatsing VDV, Heijnsdijk EAM, et al. Finding the optimal mammography screening strategy: a cost-effectiveness analysis of 920 modelled strategies. *Int J Cancer* 2022;151:287–96.
- 14 Zielonke N, Geuzinge A, Heijnsdijk EAM, on behalf of the EU-TOPIA Consortium, et al. Extending age ranges in breast cancer screening in four european countries: model estimations of harm-to-benefit ratios. *Cancers (Basel)* 2021;13:3360.
- 15 Instituto Nacional de Estadística [Internet]. Available at: <https://www.ine.es/> (19 February 2022, date last accessed)
- 16 Pataky R, Ismail Z, Coldman AJ, et al. Cost-effectiveness of annual versus biennial screening mammography for women with high mammographic breast density. *J Med Screen* 2014;21:180–8.
- 17 van den Broek JJ, van Ravestejn NT, Heijnsdijk EA, de Koning HJ. Simulating the impact of risk-based screening and treatment on breast cancer outcomes with MISCAN-Fadia. *Med Decis Making* 2018;38:54S–65S.
- 18 Degeling C, Barratt A, Aranda S, et al. Should women aged 70–74 be invited to participate in screening mammography? A report on two Australian community juries. *BMJ Open* 2018;8:e021174.
- 19 Canelo-Aybar C, Posso M, Montero N, et al. Benefits and harms of annual, biennial, or triennial breast cancer mammography screening for women at average risk of breast cancer: a systematic review for the European Commission Initiative on Breast Cancer (ECIBC). *Br J Cancer* 2022;126:673–88.