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CANCER THERAPY AND PREVENTION

The potential of breast cancer screening in Europe

Nadine Zielonke[1] | Lindy M. Kregting[1] | Eveline A. M. Heijnsdijk[1] | Piret Veerus[2] | Sirpa Heinävaara[3] | Martin McKee[4] | Inge M. C. M. de Kok[1] | Harry J. de Koning[1] | Nicolien T. van Ravesteyn[1] | the EU-TOPIA collaborators[5]

[1]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[2]National Institute for Health Development, Tallinn, Estonia
[3]Finnish Cancer Registry, Helsinki, Finland
[4]London School of Hygiene and Tropical Medicine, London, UK
[5]The EU-TOPIA collaborators are listed in the Appendix

Correspondence
Nadine Zielonke, Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Dr. Molewaterplein 40, Rotterdam 3015 GD, The Netherlands.
Email: n.zielonke@erasmusmc.nl

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Abstract

Currently, all European countries offer some form of breast cancer screening. Nevertheless, disparities exist in the status of implementation, attendance and the extent of opportunistic screening. As a result, breast cancer screening has not yet reached its full potential. We examined how many breast cancer deaths could be prevented if all European countries would biennially screen all women aged 50 to 69 for breast cancer. We calculated the number of breast cancer deaths already prevented due to screening as well as the number of breast cancer deaths which could be additionally prevented if the total examination coverage (organised plus opportunistic) would reach 100%. The calculations are based on total examination coverage in women aged 50 to 69, the annual number of breast cancer deaths for women aged 50 to 74 and the maximal possible mortality reduction from breast cancer, assuming similar effectiveness of organised and opportunistic screening. The total examination coverage ranged from 49% (East), 62% (West), 64% (North) to 69% (South). Yearly 21 680 breast cancer deaths have already been prevented due to mammography screening. If all countries would reach 100% examination coverage, 12 434 additional breast cancer deaths could be prevented annually, with the biggest potential in Eastern Europe. With maximum coverage, 23% of their breast cancer deaths could be additionally prevented, while in Western Europe it could be 21%, in Southern Europe 15% and in Northern Europe 9%. Our study illustrates that by further optimising screening coverage, the number of breast cancer deaths in Europe can be lowered substantially.

KEYWORDS
breast cancer mortality, breast cancer mortality reduction, breast cancer screening, screening coverage, screening guidelines

Abbreviations: BC, Breast cancer; CI, Confidence Interval; GDG, Guidelines Development Group; HR, Hazard Ratio; OR, odds ratio; RCT, randomised controlled trial.

1 | INTRODUCTION

Breast cancer is a major public health problem in Europe. It is by far the most frequently diagnosed neoplasm in European women and is responsible for nearly one third of all new cancer cases among women in 31 European countries in 2018.[1] Breast cancer is also the leading cause of death in European women.[1,2]

Randomised trials and several observational studies have demonstrated that systematic screening of eligible women through quality-assured population-based programmes for breast cancer reduces mortality from this disease.[3-15]

Based on this evidence, in 2003 the European Commission's Initiative on Breast cancer Guidelines Development Group (GDG) published their first guidelines for organised mammography screening programmes for early detection of breast cancer in asymptomatic women with a strong recommendation to inviting women ages 50 to 69, every 2 years.[16,17] The guidelines and recommendations have been updated and expanded regularly ever since based on updated evidence on efficacy or diagnostics, resulting in extending the recommendations to triennial or biennial screening the age-groups 45 to 49 and 70 to 74 in the context of an organised screening programme.[17]

At present, breast cancer screening programmes are well established in most European countries and all have some form of screening for breast cancer. Nevertheless, disparities exist in terms of the status of implementation, the extent to which screening programmes are organised, the invitation coverage, the coexistence with opportunistic screening activity and the attendance to screening.[18]

In order to know to which extent the European recommendations have been adopted, reports on the implementation have been published in 2007 and 2017.[3,18] It was shown here as well as in other studies that the coverage of (organised) screening is of key importance in order to tap the full public health potential in terms of reduction in mortality from breast cancer.[19,20]

However, in most European countries, opportunistic and organised screening coexist. Thus, to expect mortality reductions only from population-based screening programmes would probably lead to an underestimation of the total effectiveness of screening.

The primary aim of our study was to investigate what the effect would be of an increased or even complete breast cancer screening coverage on breast cancer mortality for each European country and if this effect differs between the four European regions. Therefore, we estimate how many breast cancer deaths have already been prevented due to screening and how many deaths could additionally be prevented if countries would screen all women in the age-group 50 to 69 years every 2 years for breast cancer with a hypothetical 100% coverage of screening in the advised target age groups. The secondary aim was to provide an overview of screening practice and the amount of organised as well as opportunistic screening in Europe.

What's new?

Breast cancer is the leading cause of death among European women. Although screening for breast cancer is available in all European countries, not all eligible women aged 50-69 get screened. Here, the authors calculated how many deaths could be prevented if screening coverage reached 100%, considering both organized and opportunistic screening. Already, screening prevents 21 680 deaths per year, and if all countries reached full examination coverage, an additional 12 434 deaths per year could be prevented across Europe.

2 | METHODS

2.1 | Data

2.1.1 | Data providers

As part of the EU-TOPIA project (TOwards imProved screening for breast, cervical and colorectal cancer In All of Europe), we collected data (see indicators listed in this section) of a recent year from over 36 data providers from 31 countries (see list of collaborators). They were either European screening organisers, researchers and/or policymakers. The data providers were contacted to collect any missing data, to correct any apparent inconsistencies and to approve on the use of it. For only a few countries (Greece, Portugal and Romania), data were completely missing despite best efforts of the authors to involve potential data providers. By utilising other data sources like published reports[3] or online databases (eg, the Cancer Mortality Database of the WHO[21] or ECIS—European Cancer Information System[22]), we filled these data gaps.

While our focus was clearly on national data, those were not available for a few countries. In Belgium, Spain, Sweden, Switzerland and the United Kingdom, health care delivery is organised at regional level with effectively independent screening programmes. Therefore, the data for the Belgian regions as well as the data for Scotland, Northern Ireland, England and Wales are presented separately in our study, while the data providers from Spain, Sweden and Switzerland could provide national estimates.

2.1.2 | Indicators

Examination coverage of organised screening

Based on the IARC Handbook of Cancer Prevention (2015),[23] we defined organised screening as screening programmes organised at the national or regional level, with an explicit policy, including an active invitation of the entire target population and monitoring of cancer occurrence in the target population. For our study, the examination coverage of organised screening was specified as the proportion (%) of the target population (here: 50- to 69-year-old women) screened in the chosen report year after invitation. For countries without a population-based programme, the proportion is zero.

Examination coverage of opportunistic screening

Opportunistic or nonorganised screening refers to all other breast cancer screening activity where individual invitations are not sent to the women in the eligible population or when women undergo a mammography outside or additionally to the (existing) screening programme.[3,23] Mammograms for symptomatic women are not counted as opportunistic screening. Generally, opportunistic screening is not monitored and is thus difficult to quantify. We asked the data providers to estimate opportunistic breast cancer screening by utilising insurance data, survey results or by providing their expert opinion. If that was not possible, we applied the mean examination coverage of opportunistic screening of the European region.

Total examination coverage

We based our calculations on the total examination coverage as the sum of both organised and opportunistic examination coverage. For countries without an organised breast cancer screening programme and no estimate of opportunistic screening, we applied the region-specific average of the total examination coverage.

Breast cancer deaths

We included the absolute number of breast cancer deaths in women aged 50 to 74 years in the report year for each country or region within a country. In addition to the recommended screening ages range 50 to 69, we included breast cancer deaths for five additional years in ages 70 to 74 to account for death occurring after the last screening round.

Mortality reduction

The maximal possible mortality reduction is taken from a recently published systematic review on breast cancer mortality reduction due to screening.[7] In this publication, the authors identified those studies among 61 included studies that provided best evidence for breast cancer mortality reduction due to screening for each European region, based on observed data.

The identified studies (Table 1) represent point estimates for breast cancer mortality reduction due to breast cancer screening for each European region. These point estimates were 33% in Finland (North), 50% in Italy (South) and 58% in the Netherlands (West). We assume those reductions to be the same across all screened age groups. No studies from Eastern Europe met the initial inclusion criteria and subsequently evidence for mortality reduction due to breast cancer screening was lacking. Consequently, for these countries, we applied the point estimate from Southern Europe as it is the medium value and because these two regions may seem fairly comparable in terms of the extent of screening coverage and the role of opportunistic screening.

2.2 | Calculations

We calculated for each country the number of breast cancer deaths which have already been prevented due to screening as well as the number of breast cancer deaths which could be additionally prevented if the total examination coverage (organised plus opportunistic) would reach 100%, assuming similar effectiveness of organised and opportunistic screening. We made four more assumptions to base our calculations on: first, that the underlying breast cancer mortality between current screening attenders and nonattenders is similar. Second, the maximal effect of breast cancer mortality reduction due to breast cancer screening differs across European regions, but is assumed to be the same in each of the region's countries, respectively. Third, the effects of breast cancer related therapy on the improvement of breast cancer specific mortality are implicitly accounted for in the level of reported breast cancer mortality and possible levels of breast cancer mortality reduction. They are also assumed to be the same in each region. And fourth, that the relationship between examination coverage and breast cancer mortality reduction is a linear one. Through linear interpolation of the point estimates from the best evidence studies for each European region, we were able to assign a potential breast cancer mortality reduction to any level of total screening coverage (calculation examples for each region are in Figure 1).

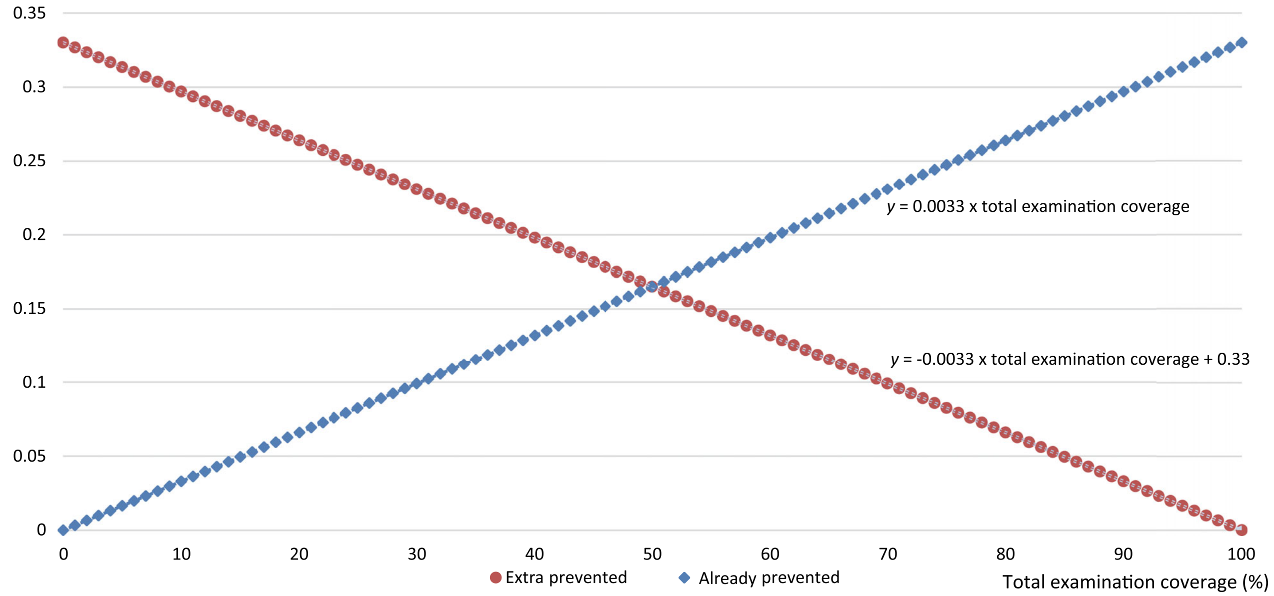
For example, based on the point estimates of breast cancer mortality reduction due to screening from the best evidence in each region (Table 1), the number of breast cancer deaths that were already prevented in a North European country would be calculated as 0.0033*total examination coverage*annual number of breast cancer deaths of women aged 50 to 74. For a South and East European country, it would be 0.005*total examination coverage*annual number of breast cancer deaths of women aged 50 to 74 and for a West European country 0.0058*total examination coverage*annual number of breast cancer deaths of women aged 50 to 74.

In contrast, the breast cancer deaths that could be additionally prevented if the screening coverage would increase to 100% is based on the number of breast cancer deaths in the absence of screening (ie, the observed number of breast cancer deaths plus the breast cancer deaths that have already been prevented). In a North European country, this number would be calculated as (−0.0033*total examination coverage + 0.33)*annual number of breast cancer deaths of women aged 50 to 74 in the absence of screening. For a South and East

TABLE 1 Overview of point estimates of breast cancer mortality reduction due to breast cancer screening from best evidence studies, per European region

Study	Region	Country	Study type	Target age	Effect sizes for breast cancer mortality[a], (95% CI)
Heinavaara et al[9]	North	Finland	Case-control	50-69	HR = 0.67 (0.49-0.90)[b]
Puliti et al[24]	South	Italy	Case-control	50-74	OR = 0.50 (0.42-0.60)[b]
Paap et al[12]	West	Netherlands	Case-control	50-75	OR = 0.42 (0.33-0.53)[b]

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio.
[a]Attenders/nonattenders.
[b]Estimates corrected for self-selection bias.



Region	breast cancer deaths already prevented	Additionally preventable breast cancer deaths
North	*y* = 0.0033 * total examination coverage	*y* = –0.0033 * total examination coverage + 0.33
South	*y* = 0.005 * total examination coverage	*y* = –0.005 * total examination coverage + 0.5
West	*y* = 0.0058 * total examination coverage	*y* = –0.0058 * total examination coverage + 0.58
East	*y* = 0.005 * total examination coverage	*y* = –0.005 * total examination coverage + 0.5

By means of this graph, the number of already prevented breast cancer deaths and additionally preventable breast cancer deaths can be derived for any possible country.
The blue line (squares) represents the interpolated trend of the already prevented breast cancer deaths when the maximal possible breast cancer mortality reduction is 33% (Northern Europe). In a hypothetical Northern European country, the total examination coverage is 60% and 3000 annual breast cancer deaths occur. These deaths need to be multiplied with the value on the y-axis resulting from the respective value on the x-axis (total examination coverage). Or alternatively. 0.0033*60=0.198 and 0.198*3,000=594. Thus, 594 women did not die of breast cancer due to current screening activity.
To calculate the corresponding number of breast cancer deaths that could be additionally prevented if the examination coverage would increase to 100%, one needs to calculate the number of breast cancer deaths in the absence of screening first (ie, the observed number of breast cancer deaths plus the breast cancer deaths that have already been prevented, thus 3,000 plus 594). Based on the total examination coverage, following the red line (circles), one can take the respective factor from the y-axis that these 3594 deaths need to be multiplied with (or alternatively, *y* = -0.0033 * total examination coverage + 0.33). Hence, we calculated the factor on the y-axis to be 0.132 (-0.0033*60+0.33) and therefore 474 additional breast cancer deaths could be prevented. For the other three European regions, the calculations should be based on the respective regional values shown in the table above.

FIGURE 1 (Potential) breast cancer mortality reduction, per total examination coverage (example region North) [Color figure can be viewed at wileyonlinelibrary.com]

European country, it would be (–0.005*total examination coverage + 0.5)*annual number of breast cancer deaths of women aged 50 to 74 in the absence of screening and for a West European country (–0.0058*total examination coverage + 0.58)*annual number of breast cancer deaths of women aged 50 to 74 in the absence of screening (Figure 1).

Despite differences in target age range and frequency, for our study all calculations were based on the hypothetical situation of a uniform policy of screening women biennially between the ages 50 and 69. The observed coverage rates were adjusted accordingly.

2.3 | Sensitivity analyses

Because of uncertainties around some assumptions made, the following sensitivity analyses were performed.

A sensitivity analysis was performed in which potential gains were calculated up to a maximal coverage of 84%, which is the highest screening coverage found in a European country (ie, Denmark).

In addition, sensitivity analyses were performed in which the effectiveness of opportunistic screening was 10%, 20%, and 30% lower than organised screening. In these analyses, the percentages that could be gained to reach an examination coverage of 100% were distributed over organised and opportunistic screening to the same distribution as was already present in the specific country [eg, if present screening coverage was 40% organised and 20% opportunistic (ratio 2:1), the additional coverage was 27% organised and 13% opportunistic (2:1)].

To assess the impact of the regional point estimates on the maximal possible breast cancer mortality reduction on the regional results of our study, we performed a sensitivity analysis where we varied the point estimates across all European countries, that is, we applied a 33% (North), a 50% (South) and a 58% (West) breast cancer mortality reduction due to screening irrespective of the location of the country.

3 | RESULTS

3.1 | Screening practice and examination coverage

Most European countries adopted the target age range for breast cancer screening as recommended by the European Commission for which there is a strong recommendation (50-69). Only a few countries adopted a different age range and either invite women younger than 50 or they invite women beyond the age of 69, while a few stop

TABLE 2 Overview of national background data used as input

Country/region	Report year	Breast cancer deaths 50-74	Examination coverage 50-69 (%)[a]		
			Organised	Opportunistic	Total
North					
Denmark	2014	521	81.1	3.0	84.1
Estonia[b]	2016	121	37.4	8.0	45.4
Finland	2014	390	78.9	3.9	82.8
Iceland	2015	25	58.7	2.0	60.7
Latvia	2016	247	26.7	8.1	34.8
Lithuania	2016	265	44.2	5.0	49.2
Norway	2016	347	72.3	5.0	77.3
Sweden[c]	2016	605	76.5	1.0	77.5
Total North		*2521*	*59.5*	*4.5*	*64.0*
West					
Austria[d]	2014	658	25.0	20.0	45.0
Wallonia (B)	2015	386	7.0	45.0	52.0
Brussels (B)	2015	69	11.6	42.0	53.6
Vlaanderen (B)	2015	736	51.0	18.2	69.2
France[c]	2015	5043	51.6	13.5	65.1
Germany	2015	7575	51.2	5.0	56.2
Ireland[e]	2015	335	53.3	3.9	57.2
Luxembourg	2013	29	56.0	5.7	61.7
Netherlands[c]	2015	1628	75.8	5.0	80.8
Switzerland	2015	616	14.5	10.5	25.0
Scotland (United Kingdom)[f,g]	2015	444	62.1	0	62.1
N. Ireland (United Kingdom)[f,g]	2016	133	81.4	0	81.4
Wales (United Kingdom)[f,g]	2016	264	76.6	0	76.6
England (United Kingdom)[f,g]	4115	4115	75.4	0	75.4
Total West		*21 972*	*49.0*	*12.1*	*61.5*
East					
Bulgaria	2015	711	–	49.0	49.0[h]
Croatia	2015	533	37.5	12.0	49.5
Czech Republic[d]	2016	823	57.6	3.0	60.6
Hungary[i]	2015	1197	22.5	19.5	42.0
Poland	2016	3421	38.7	19.9	58.6
Romania[j]	2016	1867	–	49.0	49.0[h]
Slovakia	2017	542	–	30.0	30.0
Slovenia	2015	177	40.1	13.0	53.1
Total East		*9271*	*39.3*	*16.2*	*49.0*
South					
Cyprus	2017	58	35.1	32.4[k]	63.1
Greece[j]	2016	824	–	68.9	[h]
Italy	2013	3900	42.3	19	61.3
Malta[g]	2016	40	52.9	19.5	72.4
Portugal[c,j]	2013	762	33.8	32.4[k]	66.2
Spain	2016	2644	62	19.5	81.5
Total South		*8228*	*45.2*	*32.4*	*68.9*

[a]The examination coverage of organised/opportunistic screening was specified as the proportion (%) of the target population (here: 50- to 69-year-old women) screened in the index year after invitation.
[b]Screening ages 50 to 62.
[c]Screening ages 50 to 74.
[d]Screening ages 45 to 69.
[e]Screening ages 50 to 64.
[f]No opportunistic screening activity due to The Ionising Radiation (Medical Exposure) Regulations 2017.
[g]Three-years screening interval.
[h]Total screening is average or the region.
[i]Screening ages 45 to 64.
[j]Data from ECIS,[22] Globocan[21] and the second screening report.[3]
[k]Opportunistic screening is average of the region.

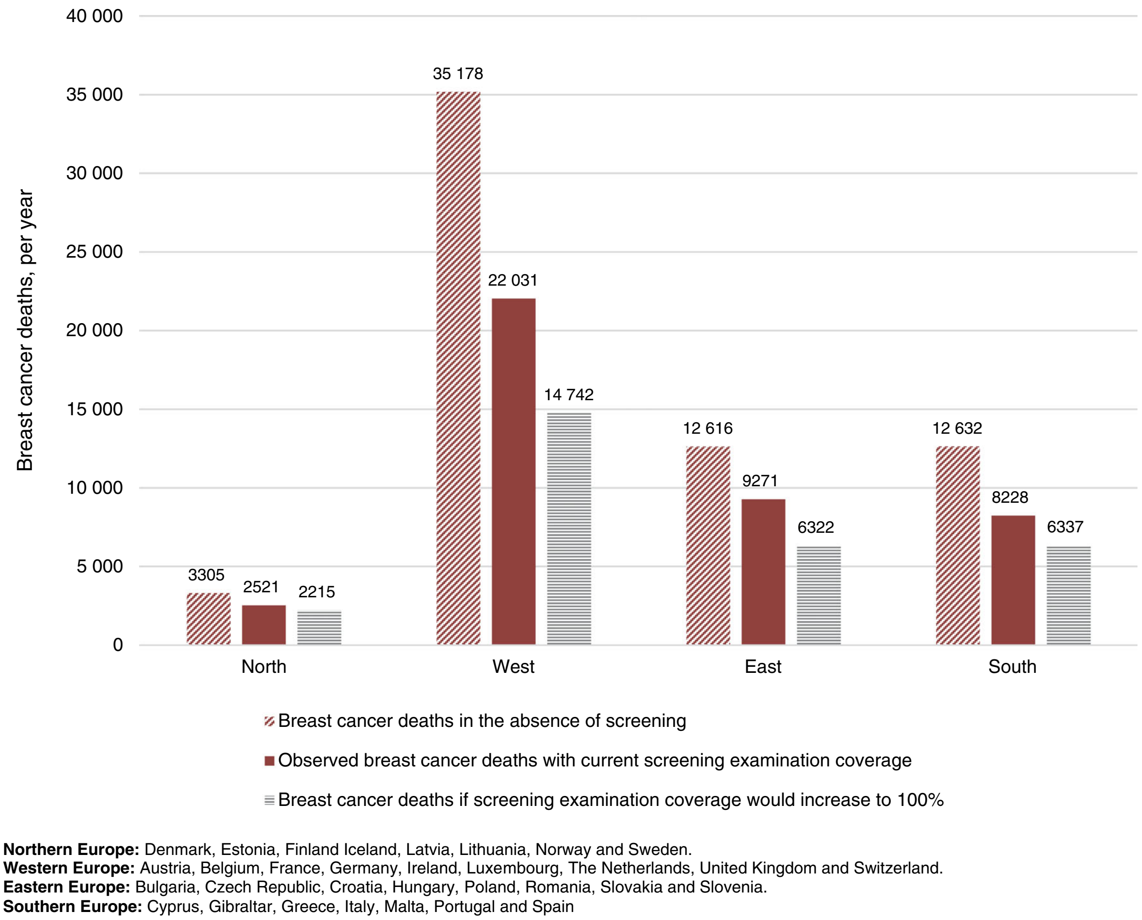


FIGURE 2 Annual number of observed and preventable breast cancer deaths, ages 50 to 74, per European region [Color figure can be viewed at wileyonlinelibrary.com]

inviting women at the age of 62 and 64, respectively. The screening interval was 2 years in all countries except for Malta and the United Kingdom where three yearly screening was practiced (Table 2).

The examination coverage of organised breast cancer screening was highest in Northern Europe and lowest in Eastern Europe (an average of 59% compared to 39%; Table 2). In contrast, the examination coverage of opportunistic screening was lowest in Northern Europe and highest in Southern Europe (5% compared to 32%). The total examination coverage ranged from 49% in Eastern Europe, 62% in Western Europe, 64% in Northern Europe to 69% in Southern Europe. With 84% and 25%, Denmark and Switzerland had the highest and the lowest total examination coverage, respectively.

3.2 | Prevented breast cancer deaths

Based on the collected data, 42 051 women die of breast cancer in Europe every year. Due to the existence of breast cancer screening, 21 680 breast cancer deaths have already been prevented annually. Consequently, with no breast cancer screening activities, 63 731 women would have died of the cancer. Thus, 34% of breast cancer specific deaths have been prevented due to mammography screening across Europe. We calculated that 12 434 breast cancer deaths could additionally be prevented annually if breast cancer screening coverage would be extended to 100%. The regional results are presented in Figure 2 where Western Europe sticks out due to its population size as well as the biggest regional point estimate of breast cancer mortality reduction. In Western Europe, 22 031 women died of breast cancer in the reported year (red column). Due to the average total examination coverage of 61.5%, 13 147 breast cancer deaths were already averted. Hence, in the absence of screening, 35 178 women would have died annually of breast cancer (red striped column). If screening coverage would increase to 100%, only 14 742 breast cancer deaths would occur (gray striped column) as 7298 additional breast cancer deaths could be averted annually. The respective numbers for all European countries and regions are presented in Table 3. Figure 3 presents the relative effect of a 100% total examination coverage for each country, that is, showing the share of breast cancer deaths that could additionally be prevented when countries would screen all women 50 to 69 years of age every 2 years. Most countries could potentially avert additional 20% to 29% of their breast cancer deaths. In contrast, all Nordic countries have consistently high coverage rates through their organised programmes and less additional breast cancer deaths could potentially be prevented when screening would be extended to 100%.

TABLE 3 Number of (non-)preventable breast cancer deaths, and the results of the sensitivity analysis

	Prevented breast cancer deaths					Sensitivity analysis: Max. European coverage		Sens −10%[a]		Sens−20%[a]		Sens−30%[a]		Max West[b]		Max North[b]		Max South[b]	
	A # BC deaths already prevented due to current screening coverage	B # BC deaths prevented if screening coverage would increase to 100	C # BC deaths in the absence of screening	A/C	B/C	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 84%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%
North																			
Denmark	200	38	721	28%	5%	200	0	199	38	198	37	197	37	496	94	200	38	378	72
Estonia	21	26	142	15%	18%	21	18	21	25	20	25	20	24	43	52	21	26	36	43
Finland	147	30	537	27%	6%	147	2	146	30	146	30	146	30	360	74	147	30	276	57
Iceland	6	4	31	20%	13%	6	2	6	4	6	4	6	4	14	9	6	4	11	7
Latvia	32	60	279	11%	21%	32	45	31	58	31	57	31	56	62	117	32	60	52	97
Lithuania	51	53	316	16%	17%	51	42	51	53	50	52	49	51	106	110	51	53	86	90
Norway	119	35	466	26%	8%	119	11	117	34	116	33	116	33	282	84	119	35	219	65
Sweden	208	59	813	26%	7%	208	16	209	59	209	59	208	59	494	140	208	59	383	109
Total	784	306	3305	24%	9%	784	136	780	301	777	297	773	294	1858	680	784	306	1440	539
Comp. base case							*45%*		*98%*		*97%*		*96%*		*223%*		*100%*		*176%*
West																			
Austria	232	284	890	26%	32%	232	201	216	266	200	250	185	234	232	284	115	140	191	181
Wallonia (B)	167	154	553	30%	28%	167	103	147	135	129	118	137	107	167	154	80	74	136	125
Brussels (B)	31	27	100	31%	27%	31	17	28	24	23	21	22	19	31	27	15	13	25	22
Vlaanderen (B)	493	221	1229	40%	18%	493	107	472	212	454	203	438	195	493	221	218	98	389	174
France	3059	1645	8102	38%	20%	3059	893	3002	1600	2711	1511	2665	1471	3059	1645	1380	742	2434	1308
Germany	3663	2868	11 238	33%	26%	3663	1825	3604	2827	3562	2790	3523	2755	3663	2868	1725	1350	2960	2318
Ireland	166	125	501	33%	25%	166	79	164	124	163	122	161	121	166	125	78	59	134	101
Luxembourg	16	10	45	36%	22%	16	6	16	10	16	10	16	10	16	10	7	5	13	8
The Netherlands	1436	338	3064	47%	11%	1436	53	1424	335	1411	331	1400	328	1436	338	592	139	1104	259
Switzerland	104	313	720	15%	44%	104	247	104	296	99	281	95	267	104	313	55	166	88	264
Scotland (United Kingdom)	250	153	694	36%	22%	249	89	250	138	250	122	250	107	250	153	114	70	200	122
N, Ireland (United Kingdom)	119	28	252	47%	11%	119	3	119	25	119	22	119	19	119	28	49	11	91	21
Wales (United Kingdom)	211	63	475	44%	13%	211	19	211	57	211	51	211	44	211	63	89	27	164	49
England (United Kingdom)	3198	1060	7313	44%	15%	3198	339	3198	954	3198	848	3198	742	3198	1060	1363	452	2490	826
Total	13 147	7289	35 178	37%	21%	13 146	3981	12 954	7003	12 545	6682	12 421	6420	13 147	7289	5880	3345	10 419	5779
Comp. base case							*55%*		*96%*		*92%*		*88%*		*100%*		*46%*		*79%*

TABLE 3 (Continued)

	Prevented breast cancer deaths					Sensitivity analysis: Max. European coverage		Sens −10%[a]		Sens−20%[a]		Sens−30%[a]		Max West[b]		Max North[b]		Max South[b]	
	A # BC deaths already prevented due to current screening coverage	B # BC deaths prevented if screening coverage would increase to 100	C # BC deaths in the absence of screening	A/C	B/C	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 84%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%	# BC deaths already prevented due to current screening coverage	# BC deaths prevented if screening coverage would increase to 100%
East																			
Bulgaria	231	240	942	24%	26%	231	160	201	205	173	177	193	158	282	288	137	140	231	235
Croatia	175	177	708	25%	25%	175	120	172	172	166	166	162	161	215	217	104	105	175	177
Czech Republic	358	230	1181	30%	20%	358	136	358	229	355	227	353	226	446	287	206	132	358	230
Hungary	318	439	1515	21%	29%	318	318	307	416	304	395	301	374	385	532	193	266	318	439
Poland	1418	992	4839	29%	21%	1418	605	1436	962	1370	915	1309	870	1761	1232	820	574	1418	992
Romania	605	630	2472	24%	26%	605	420	650	566	543	482	448	405	741	756	360	367	605	618
Slovakia	176	183	718	24%	26%	176	194	96	201	83	175	70	150	114	263	60	137	96	220
Slovenia	64	57	241	27%	24%	64	14	74	56	71	54	69	52	79	70	38	33	64	57
Total	3345	2949	12 616	27%	23%	3345	1968	3293	2807	3065	2592	2905	2397	4023	3645	1917	1755	3264	2969
Comp. base case							*67%*		*95%*		*88%*		*81%*		*124%*		*60%*		*101%*
South																			
Cyprus	29	14	87	33%	17%	29	9	27	15	25	14	25	13	37	20	16	9	29	16
Greece	433	176	1257	34%	14%	433	75	387	153	328	129	274	108	549	223	243	99	433	176
Italy	1724	1097	5624	31%	20%	1724	647	1641	1047	1574	1002	1511	958	2152	1369	989	629	1724	1097
Malta	23	9	63	36%	14%	23	10	22	8	21	8	20	8	29	11	13	5	23	9
Portugal	377	194	1139	33%	17%	377	103	312	173	293	161	275	150	475	244	213	109	377	194
Spain	1818	402	4462	41%	9%	1818	45	1239	342	1205	331	1171	320	2370	523	973	215	1818	402
	4404	1891	12 632	35%	15%	4404	888	3629	1738	3445	1645	3276	1556	5611	2391	2446	1066	4404	1893
							47%		*92%*		*87%*		*82%*		*126%*		*56%*		*100%*
ALL	21 680	12 434	63 731	34%	20%	21 680	6973	20 657	11 849	19 832	11 215	19 375	10 667	24 639	14 005	11 028	6472	19 528	11 180
Comp. base case						*100%*	*56%*	*95%*	*95%*	*91%*	*90%*	*89%*	*86%*	*114%*	*113%*	*51%*	*52%*	*90%*	*90%*

Abbreviation: BC, breast cancer.

[a]Effectiveness of opportunistic screening to lower cancer specific mortality was set to be 10%, 20% and 30% lower than organised screening. In these analyses, the gained percentages of screening coverage (up to 100%) were distributed over organised and opportunistic screening to the same distribution as was already present in the specific country [eg, if present screening coverage was 40% organised and 20% opportunistic (ratio 2:1), the additional coverage was 27% organised and 13% opportunistic (2:1)].

[b]Application of each of the regional point estimates across all European countries, that is, we applied a 58% (West), a 33% (North) and a 50% (South) breast cancer mortality reduction due to screening irrespective of the location of the country.

3.3 | Sensitivity analyses

As shown in Table 3, assuming a maximal coverage of 84% instead of 100% led to a significant drop in prevented breast cancer deaths (6975 averted deaths compared to 12 438). This cut is predominantly explained by countries who already have a comparably high screening coverage and lose the additional benefit of increasing up to 100% (eg, the Netherlands, Spain or Denmark).

Assuming that opportunistic screening is 10% less effective as organised screening led to a 5% reduction of the additionally preventable breast cancer deaths. A 20% and 30% lowered effectiveness led to a 10% and 14% reduction, respectively. The effect was biggest in countries with a high percentage of opportunistic screening (eg, Wallonia/Belgium). Applying the Western European point estimate for mortality reduction across all of Europe, breast cancer deaths already prevented increased by 14% and breast cancer deaths that can additionally be prevented increased by 13%. This analysis has the biggest impact for Northern Europe (plus 223%), where the point estimate was the smallest in the base analysis. When the estimates from Northern and Southern Europe were applied, the number of breast cancer deaths prevented decreased by 49% and 10%, while the additionally preventable breast cancer deaths decreased by 48% and 10%, respectively, compared to the base calculation.

4 | DISCUSSION

Our study illustrates how breast cancer screening in Europe already has a substantial impact by preventing nearly 21 700 breast cancer deaths per year. In addition, through further optimising screening coverage, the number of breast cancer deaths of European women could be further reduced significantly. The effect would be particularly notable in Eastern and Western Europe. Thus, rolling-out a breast cancer screening programme with complete coverage across the country is

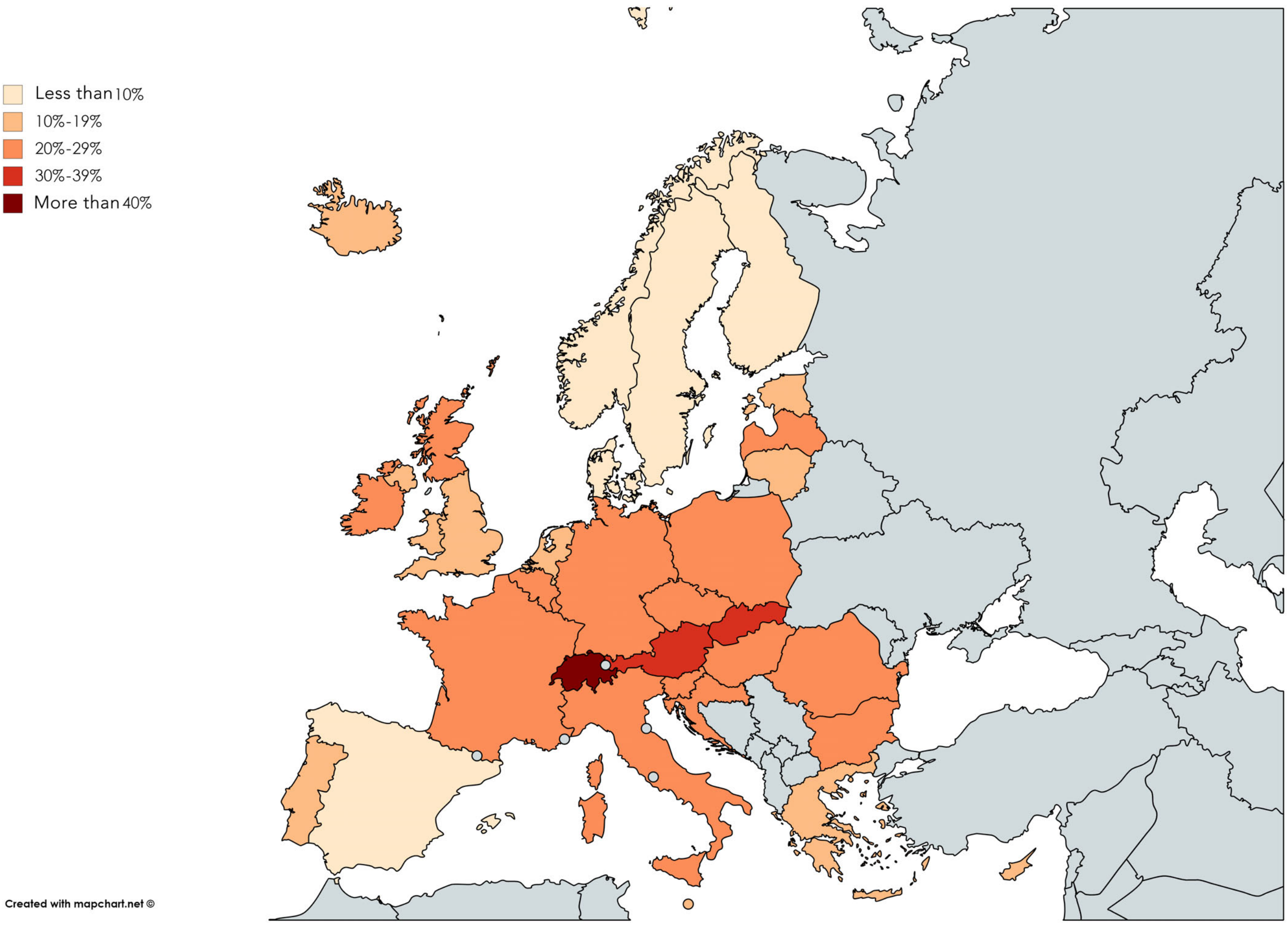


FIGURE 3 Percentage of breast cancer deaths that could be additionally prevented if examination coverage would increase to 100%, per European country*. *Belgium is depicted as one country whereas in the calculation three highly autonomous regions Flanders, Wallonia and Brussels are included. These regions have very disparate screening programs for breast cancer (see Table 2) resulting in very different effects of an increased total examination coverage (Table 3). Only 8 of the 26 Swiss cantons have organised breast cancer screening programmes which causes substantial variation in the distribution of organised vs opportunistic screening across regions. On a national level, total examination coverage was only 25% in 2015 (14% organised and 11% opportunistic) according to the national expert. Thus, a national examination coverage of 100% would further reduce breast cancer deaths by 44% [Color figure can be viewed at wileyonlinelibrary.com]

particularly favourable for Swiss women as it would further reduce breast cancer deaths by 44%. In contrast, all Nordic countries have consistently high coverage rates through their organised programmes (between 72% and 81%) plus a very low coverage of opportunistic screening for breast cancer (between 1% and 5%). When the total examination coverage for women aged 50 to 69 is already as high as 84%, not many additional breast cancer deaths could potentially be prevented if screening was extended to 100%.

Screening provides both harms and benefits, and therefore it is important to ensure a good balance between the two. Information on the balances of benefits and harms is needed to demonstrate that a chosen screening policy and programme with all its components and protocols is appropriate for any given country. In this article, however, we focus solely on the primary aim of (organised) breast screening which is to reduce mortality from breast cancer through early detection.[16,20]

The calculations for this present analysis are based on the assumption that opportunistic and organised breast cancer screening can lead to the same level of cancer specific mortality reduction. However, past studies resulted in slightly conflictive results. For example, a study in Denmark found that the sensitivity was twice as high for organised screening, while the specificity of organised and opportunistic screening was found to be similar.[25] Hofvind et al compared opportunistic breast cancer screening in Vermont (United States) with organised breast cancer screening in Norway.[26] Both screening systems detected cancer at about the same rate and at the same prognostic stage. A study from Switzerland found that there was little difference in stage distribution and detection rates between cantons with only opportunistic screening and cantons with both organised and opportunistic screening,[27] indicating that both are similarly effective. It was noted, however, that the quality of opportunistic screening in Switzerland probably benefitted from the training of radiographers, a higher reading volume of radiologists and the technical and quality-controlled procedures of the organised programme.

In summary, the main differences between organised and opportunistic screening can be seen in attendance,[28] equity,[28] and cost-effectiveness[29] which are all (much) better in organised screening. With regards to quality aspects, opportunistic screening might be quite similar to that of organised screening. Moreover, since opportunistic screening takes place next to organised screening in most countries (Bulgaria, Romania, Slovakia and Greece being the exception), it can profit from advantages of the organised system. Consequently, we are confident that by conflating opportunistic and organised screening for calculations and argumentations, we can increase the relevance of this article.

The European guidelines for quality assurance in breast cancer screening and diagnosis consider participation rates above 70% as acceptable and above 75% as desirable.[30] In line with those guidelines, we do not actually propagate a screening coverage of 100% as this probably conflicts with informed choice.[31] However, by basing our calculations on a hypothetical goal of a screening coverage of 100% of eligible women, we assessed the maximum potential of breast cancer screening for each country.

Our study focuses on screening women ages 50 to 69 as this is currently the practice in most European countries. Despite some exceptions (Table 2), women aged 70 to 74 are usually not eligible for mammography screening because there was insufficient evidence that screening would reduce mortality for women in this age group. Previous randomised controlled trials (RCTs) and observational studies on breast cancer screening have not generally included women aged 70 years and over. In their newest (conditional) screening recommendations, however, the European Commission Initiative on Breast Cancer suggests that average-risk and asymptomatic women between 45 and 49, as well as between 70 and 74 years old, have mammography screening for breast cancer.

Several further considerations inform the interpretation of our study. There is an ongoing debate as to which study design is the gold standard for estimating the true effect of screening on cancer-specific mortality.[23,32,33] For our study, we considered that high-quality case-control studies[7] provide the most informative data. RCTs were conducted more than 20 years ago when adherence to screening was less and the quality of screening programmes and breast cancer care were less advanced than today. In contrast, observational studies of screening are known to be prone to bias as there is no unselected unscreened group. Women who do not participate in screening might have a higher a priori risk of breast cancer mortality. If that was so, our assumption of a proportional relationship between screening coverage and reduction in breast cancer mortality would not hold. Therefore, it was of particular importance to base our analysis on estimates of mortality reduction that were not influenced by self-selection bias.

The regional point estimates from individual studies on mortality reduction due to breast cancer screening, which our calculations are based on, differ quite significantly. These differences indicate differences in evaluation designs, in target ages, in ages of follow-up of breast cancer incidence or mortality, in duration of follow-up since first invitation, in comparison groups and in assessment methods of self-selection bias.[7,9,12,24] Therefore, the region-specific point estimates are not directly comparable with each other and they should not be used as a 'quality indicator' for organised breast cancer screening in each region.

Despite the different effect sizes, we are confident that our three regional estimates do not present an overestimation of the benefit of mammographic screening. They are well in the range of an analysis of Broeders et al from 2012[5] who present a pooled breast cancer mortality reduction for women who actually participated in screening of 38% based on incidence based mortality studies [odds ratio (OR) = 0.62 (0.56-0.69)] and 48% based on case-control studies [OR = 0.52 (0.42-0.65), adjusted for self-selection]. An analysis similar to our study has been published in 2013. Mackenbach and McKee[34] estimated there would be over 17 000 fewer breast cancer deaths each year if all countries in the EU could reduce death rates to those in the best performing country, Sweden. However, our study was based on cause- and age-specific death rates only rather than the combination of cause- and age-specific mortality and the extent of screening activity.

To our knowledge, there have been no other studies so far that have estimated the effect of breast cancer screening on cancer-specific mortality when brought to its full potential based on the total extent of breast cancer screening activities in Europe. We were able to provide an extensive overview of the amount of organised as well as opportunistic screening in Europe by consulting national experts. Accordingly, some of the national estimates on screening uptake have never been published before. However, our study also has some potential limitations. The first limitation is the uncertainty regarding the coverage of opportunistic screening as these numbers are based on expert opinion or on national extrapolations of regional observations. Second, because the organised breast cancer screening in the United Kingdom as well as Malta is triennially rather than every 2 years, this led to a slight overestimation of the breast cancer death prevented. Third, our calculations probably led to an underestimation of the already prevented and additionally preventable deaths for the few countries which invite and screen women that are younger than 50 or older than 69. The fourth limitation is the fact that the number of breast cancer deaths and the estimates of examination coverage come from the same report year although the most recent breast cancer deaths rather reflect the past (eg, 5-10 years ago) than current screening practice.

Our analysis paves the way for further research as it could potentially be applied to the other two cancer sites for which the European Council recommends screening: cervical and colorectal cancer.

Our study illustrates that by further optimising screening coverage, the number of breast cancer deaths in Europe could be lowered substantially. Therefore, countries which do not yet offer organised screening for the target age range of 50 to 69 should strongly consider it based on our results. In addition, even when programmes to screen for breast cancer exist, much remains to be done. This includes increasing screening coverage through evidence-based interventions[35,36] and removing barriers to effective breast cancer screening.[37,38]

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CONFLICT OF INTEREST

H. J. d. K. reports personal fees from the University of Zurich/MSD. All other authors of this paper report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Nadine Zielonke https://orcid.org/0000-0001-6148-2371
Eveline A. M. Heijnsdijk https://orcid.org/0000-0002-4890-6069
Inge M. C. M. de Kok https://orcid.org/0000-0002-9419-0452
Harry J. de Koning https://orcid.org/0000-0003-4682-3646

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APPENDIX: EU-TOPIA COLLABORATORS

TABLE A1 EU-TOPIA collaborators

Austria	Gerald Gredinger[1]
Belgium (national)	Cancer registry (I. De Brabander[1]), Sciensano (M. Arbyn,[1] C. Simoens[1])
Belgium—Flanders	P. Martens[1]
Belgium—Wallonia	Michel Candeur[1]
Belgium—Brussel	Marc Arbyn[1], Cindy Simoens[1], JB. Burrion[1]
Bulgaria	Plamen Dimitrov[1], Zdravka Valerianova[1]
Croatia	Andrea Supe[1]
Czech Republic	Ondřej Ngo[1], Ondřej Májek[1]
Denmark	Elisabeth Lynge[1]
Estonia	Piret Veerus[2]
Finland	Sirpa Heinävaara[2], Ahti Anttila, Tytti Sarkeala
France	Agnes Rogel[1]
Germany	Vanessa Kääb-Sanyal[1], Klaus Kraywinkel[1]
Hungary	Marcell Csanadi[2], György Széles, Zoltan Voko
Italy	Carlo Senore[2], Nereo Segnan
Iceland	Rún Friðriksdóttir[1]
Ireland	Patricia Fitzpatrick[1]
Latvia	Inga Brokere[1]
Lithuania	Jurgita Grigariene[1]
Luxembourg	Diane Pivot[1]
Malta	Stephanie Xuereb[1]
The Netherlands	Linda de Munck[1], Inge de Kok, Andrea Gini, Eveline Heijnsdijk, Erik Jansen, Harry de Koning, Iris Lansdorp – Vogelaar, Nicolien van Ravesteyn
Norway	Solveig Hofvind[1]
Poland	Anna Macios[1]
Spain	Nieves Ascunce Elizaga[1]
Slovakia	Soňa Senderáková[1]
Slovenia	Katja Jarm[2], Urska Ivanus, Dominika Novak Mlakar
Sweden	Lennarth Nyström[1]
Switzerland	Jean-Luc Bulliard[1]
United Kingdom—Scotland	John Quinn[1]
United Kingdom—Northern Ireland	Jeni Rosborough[1]
United Kingdom—Wales	Ardiana Gjini[1]
United Kingdom—England	Radoslav Latinovic[1], Martin McKee

[1]Data providers.
[2]EU-TOPIA consortium members (or both).