Risks & benefits of cancer screening programmes

SAPEA report
Technical working group LC screening
EU-US Taskforce on Cancer Health Cooperation
Scientific committee EUCanScreen
PI ROBINSCA & 4-IN THE LUNG RUN TRIAL & CISNET breast & lung models

Erasmus MC, Rotterdam, The Netherlands

The new criteria for implementation of screening

Substantial positive health outcomes

- life-years gained
- improvements to cognitive, motor and/or sociol-emotional development
- significant increase in management or treatment options

Effects established with certainty, preferably in RCTs

Limited adverse side-effects

- extent of early detection, overdiagnosis and side-effects estimated
- quality-adjusted life-years gained

Anticipated balance clarified prior to participation

Reasonable ratio between costs and benefits

Implementation will not lead to substantial unintended effects

Other developments do not change this ratio in the short run

Side-effects

- False positives

- Earlier (knowledge of) diagnosis
- Earlier (and during a longer time frame) side-effects of treatment

- Early detection, but no benefit
- Extra detection (overdiagnosis), and overtreatment

- Risks of screening and assessment, and unintended detection of other diseases

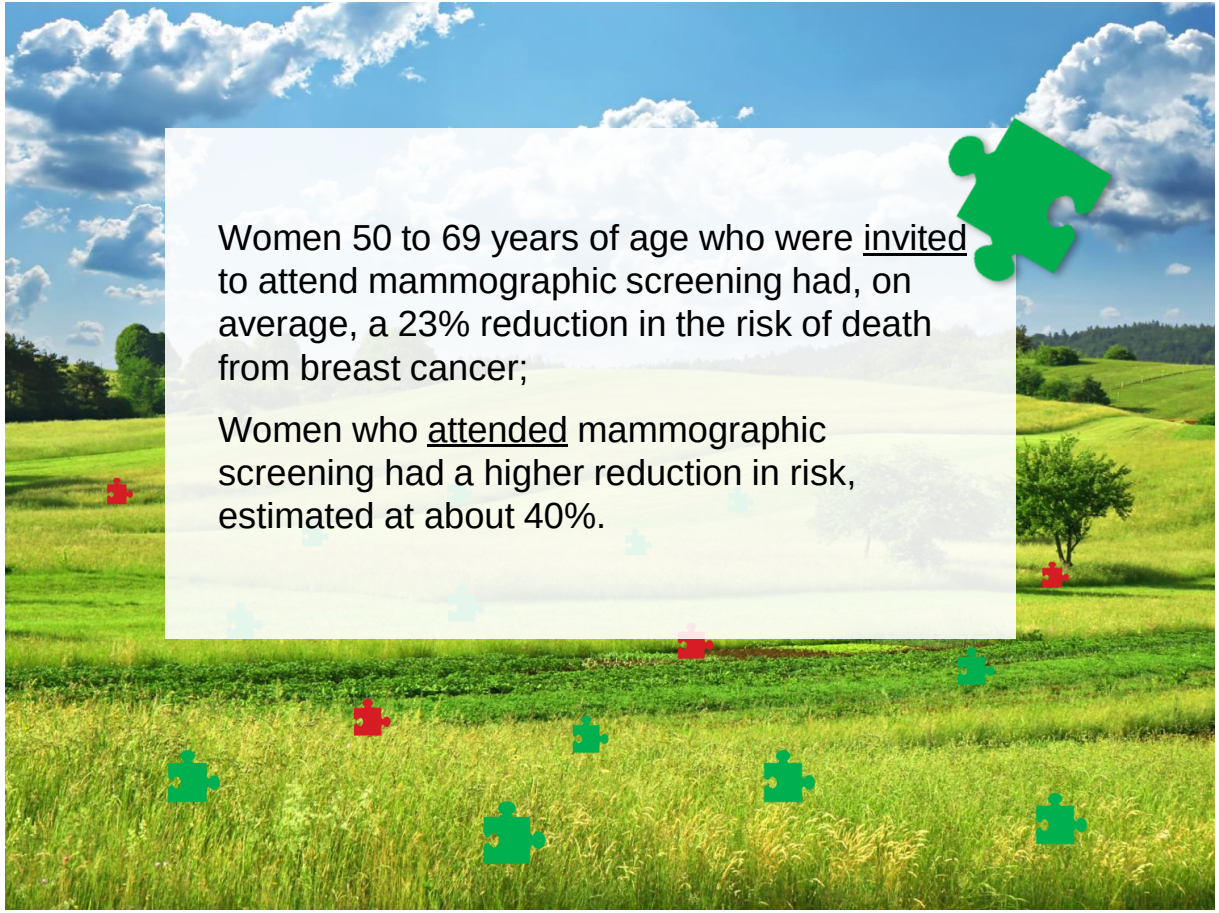
- Possible false-reassurance
- Possible licence to continue or take up bad habits
  (e.g., smoke, physical exercise, alcohol and drug intake)

What is the evidence of benefit from established (BC, CRC, CC) cancer screening programmes?

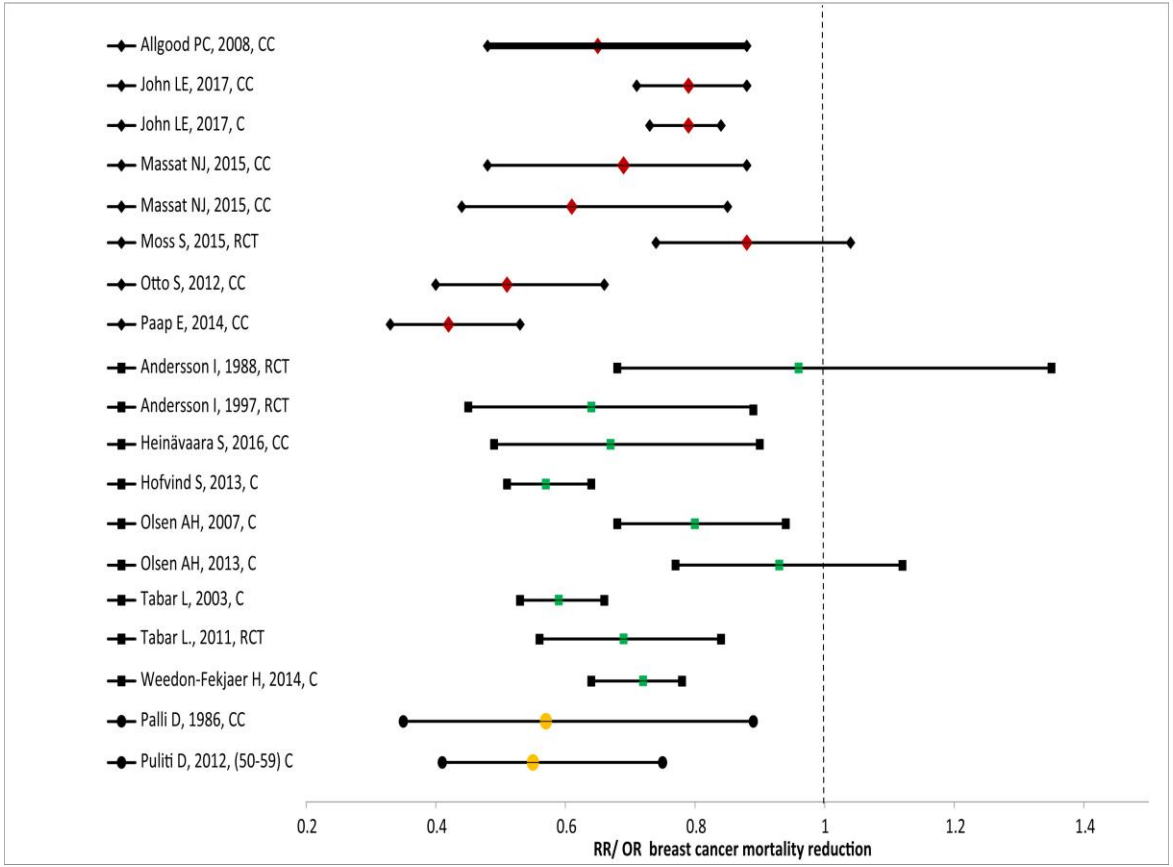
Evaluation of breast cancer screening with mammography

Age range (years)	Reduction in breast cancer mortality	
	Efficacy	Effectiveness
40–44	Inadequate	Limited
45–49		Limited
50–69	Sufficient	Sufficient
70–74	Inadequate	Sufficient
Optimal Screening Interval	Inadequate	No data

Lauby-Secretan et al. & Handbook Working Group. International Agency for Research on Cancer. Breast-cancer screening--viewpoint of the IARC Working Group. **N Engl J Med 2015**;372:2353-8


Women 50 to 69 years of age who were invited to attend mammographic screening had, on average, a 23% reduction in the risk of death from breast cancer;
Women who attended mammographic screening had a higher reduction in risk, estimated at about 40%.

Breast cancer screening



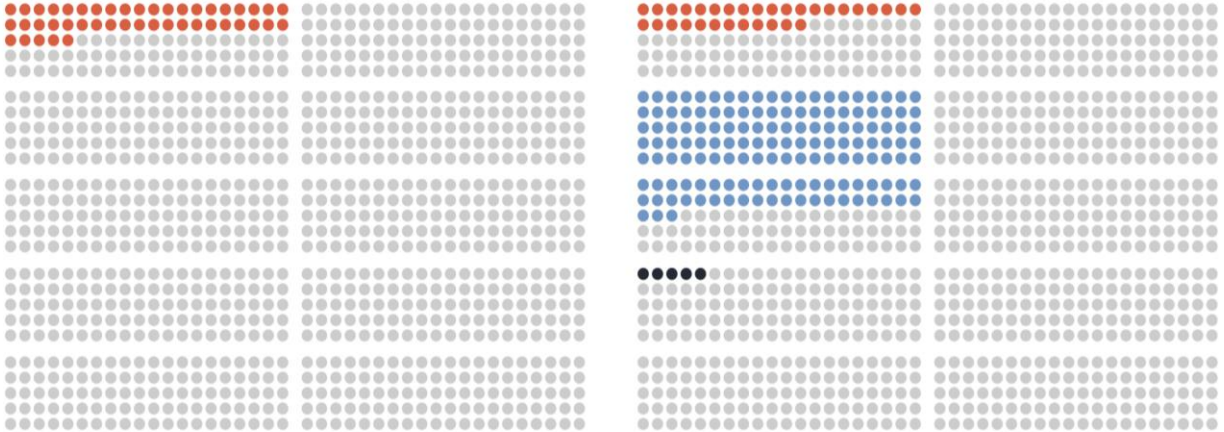
Nadine Zielonke et al., European Journal of Cancer
Volume 127 Pages 191-206
(March 2020)
DOI: 10.1016/j.ejca.2019.12.010

Mammography screening in the Netherlands

Model estimates for women aged 40 years and older who were invited to screening between 50 and 74 years, followed over their lifetimes (participation rate: 80%).

1000 women without screening

1000 women with screening



	Without screening	With screening
Women who died from breast cancer	45	32
Women with a false-positive test result	-	143
Women who were unnecessarily diagnosed and treated	-	5
Remaining women	955	820

In the Netherlands, in every 3 breast cancer deaths prevented,

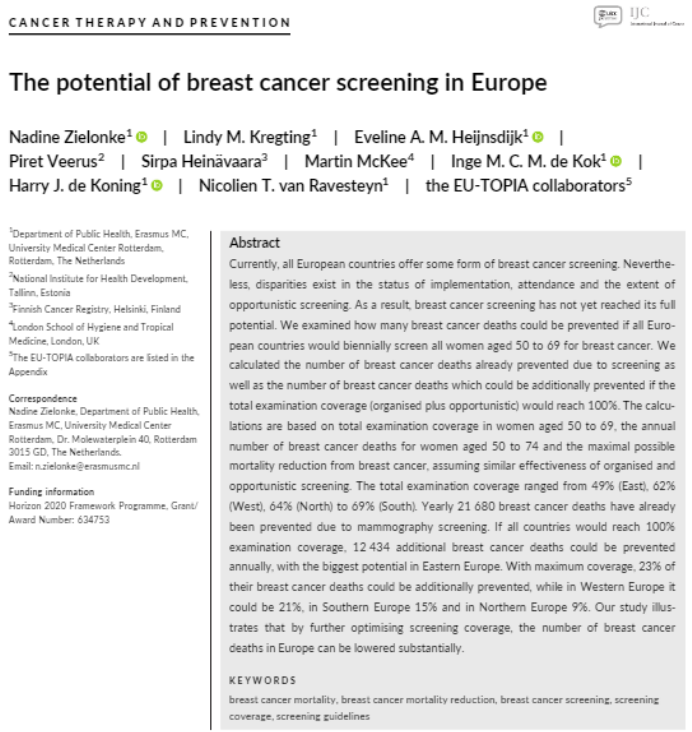
1 woman is over-diagnosed

Without over-detection,

there is no benefit

- These analyses illustrate that breast cancer screening in Europe already has a substantial impact by preventing nearly 21,700 breast cance deaths per year.

- Through introducing a hypothetical 100% coverage of screening in the advised target age groups, the number of breast cancer deaths of European women could be further reduced by almost 12,500 per year.



CANCER THERAPY AND PREVENTION

The potential of breast cancer screening in Europe

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[2]National Institute for Health Development, Tallinn, Estonia
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[5]The EU-TOPIA collaborators are listed in the Appendix

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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

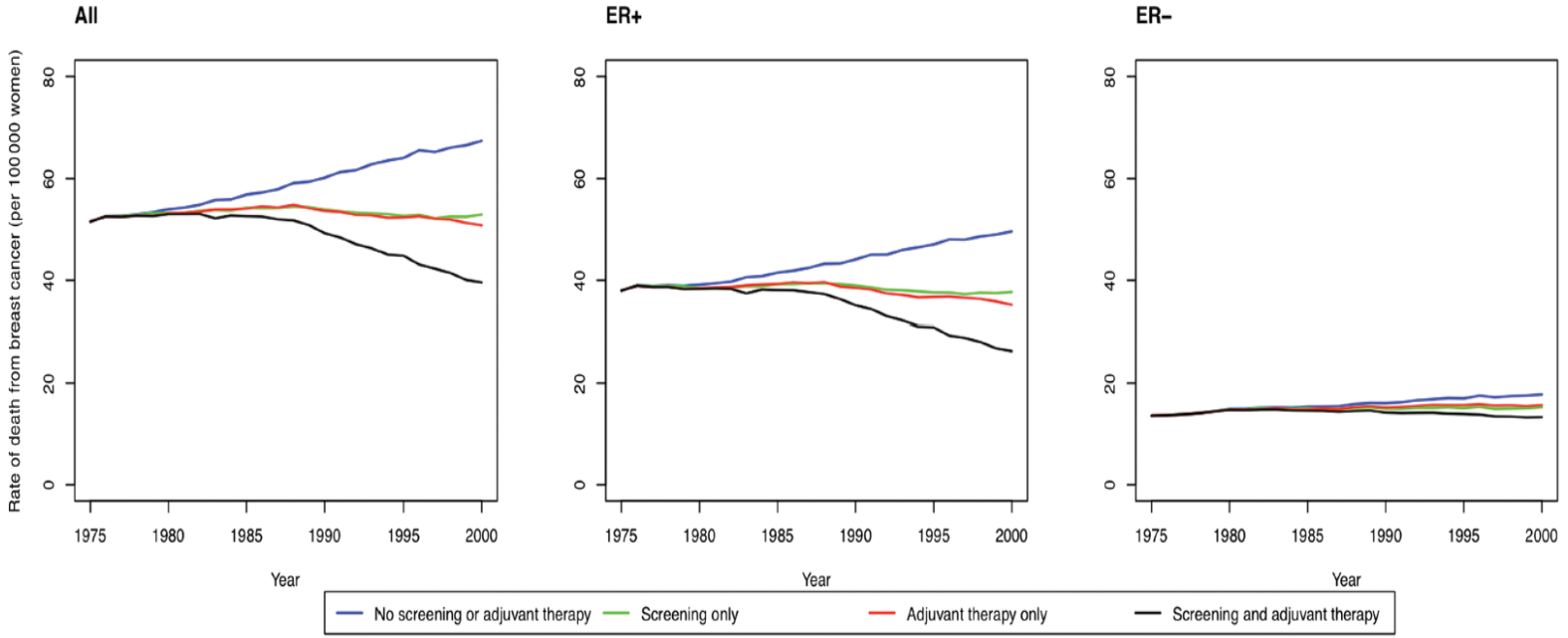


Figure 2. Predicted US overall and estrogen receptor (ER)–specific breast cancer mortality rates under counterfactual scenarios that include no screening and no adjuvant therapy, screening only, adjuvant therapy only, in comparison to screening and adjuvant treatment, for representative model (Model S).

Effects of Screening and Systemic Adjuvant Therapy on ER-Specific US Breast Cancer Mortality

JNCI 2014

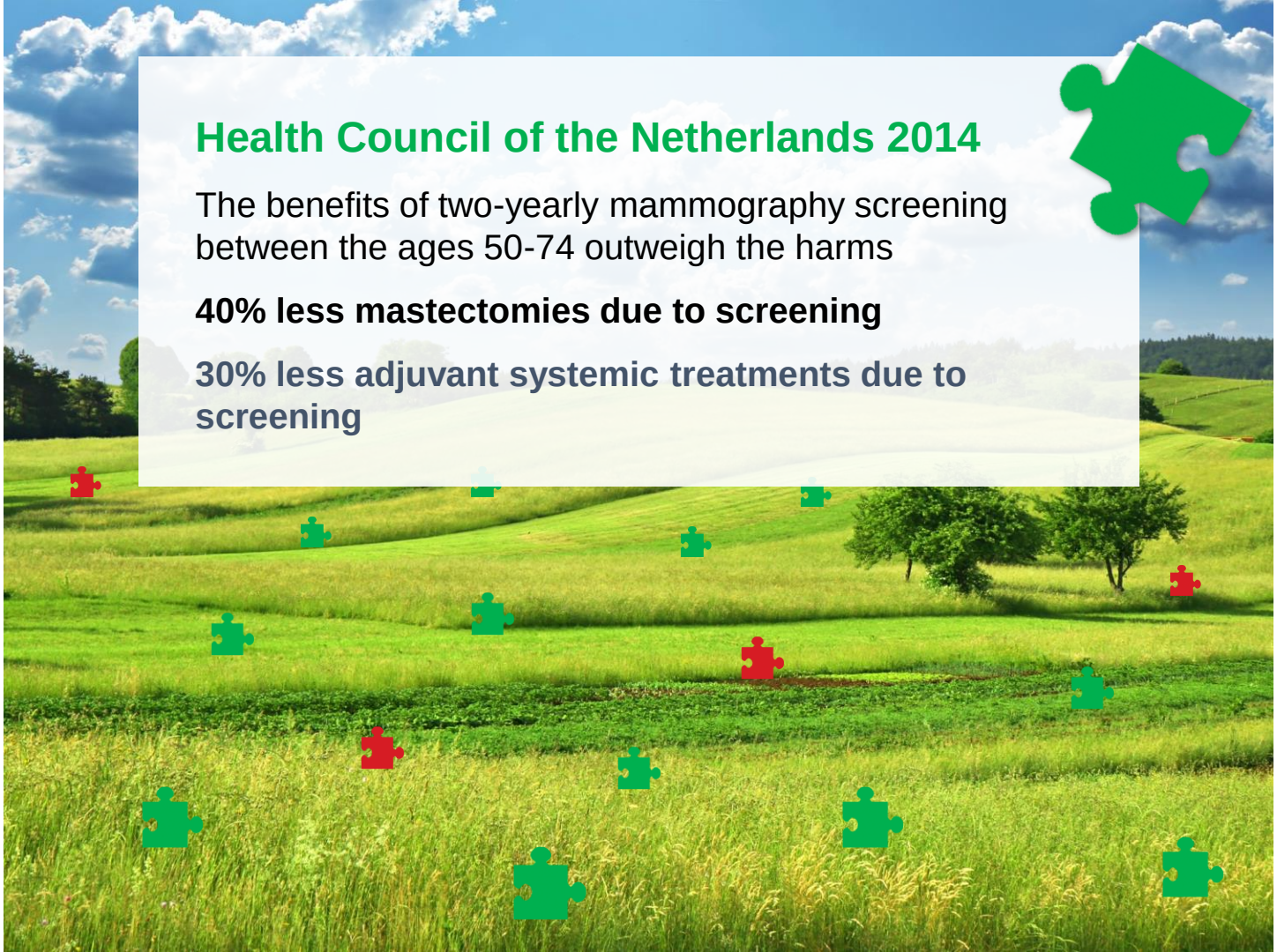
Diego Munoz, Aimee M. Near, Nicolien T. van Ravesteyn, Sandra J. Lee, Clyde B. Schechter, Oguzhan Alagoz, Donald A. Berry, Elizabeth S. Burnside, Yaojen Chang, Gary Chisholm, Harry J. de Koning, Mehmet Ali Ergun, Eveline A. M. Heijnsdijk, Hui Huang, Natasha K. Stout, Brian L. Sprague, Amy Trentham-Dietz, Jeanne S. Mandelblatt*, Sylvia K. Plevritis*

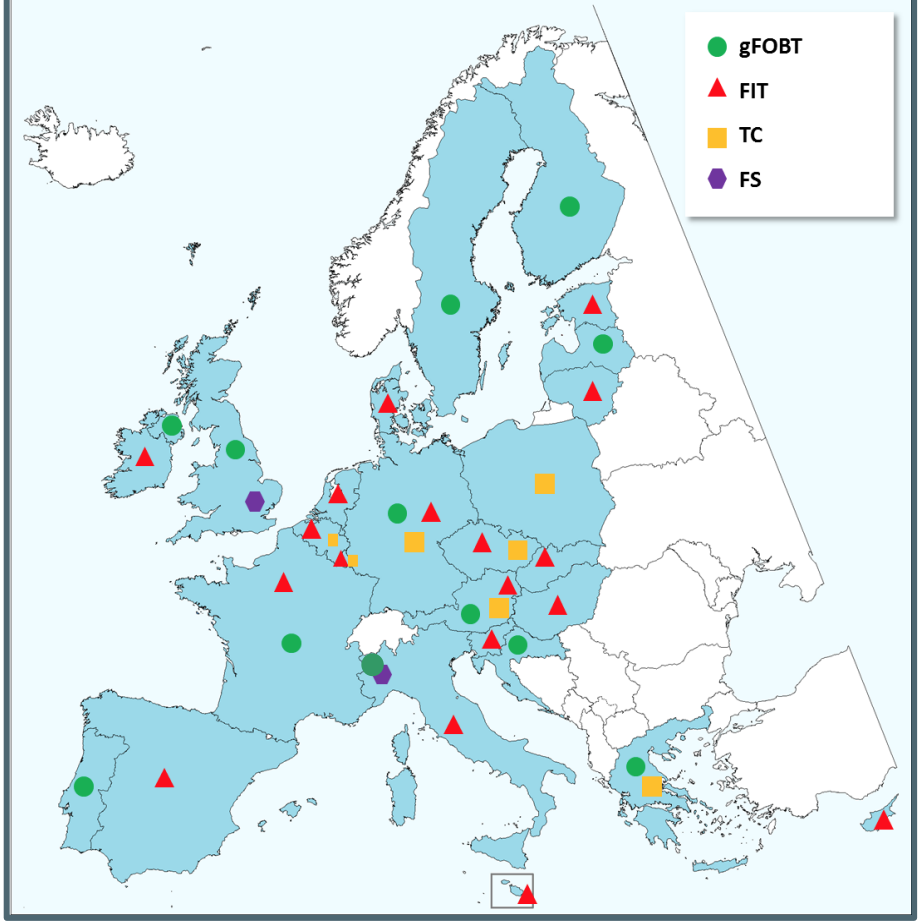
ARTICLE

Independent Prognostic Value of Screen Detection in Invasive Breast Cancer

J Natl Cancer Inst 2011;103:1–13

Stella Mook, Laura J. Van 't Veer, Emiel J. Rutgers, Peter M. Ravdin, Anthonie O. van de Velde, Flora E. van Leeuwen, Otto Visser, Marjanka K. Schmidt


Health Council of the Netherlands 2014
The benefits of two-yearly mammography screening between the ages 50-74 outweigh the harms
40% less mastectomies due to screening
30% less adjuvant systemic treatments due to screening



Tests Used for CRC Screening In the EU Member States

Intermediate outcome measures

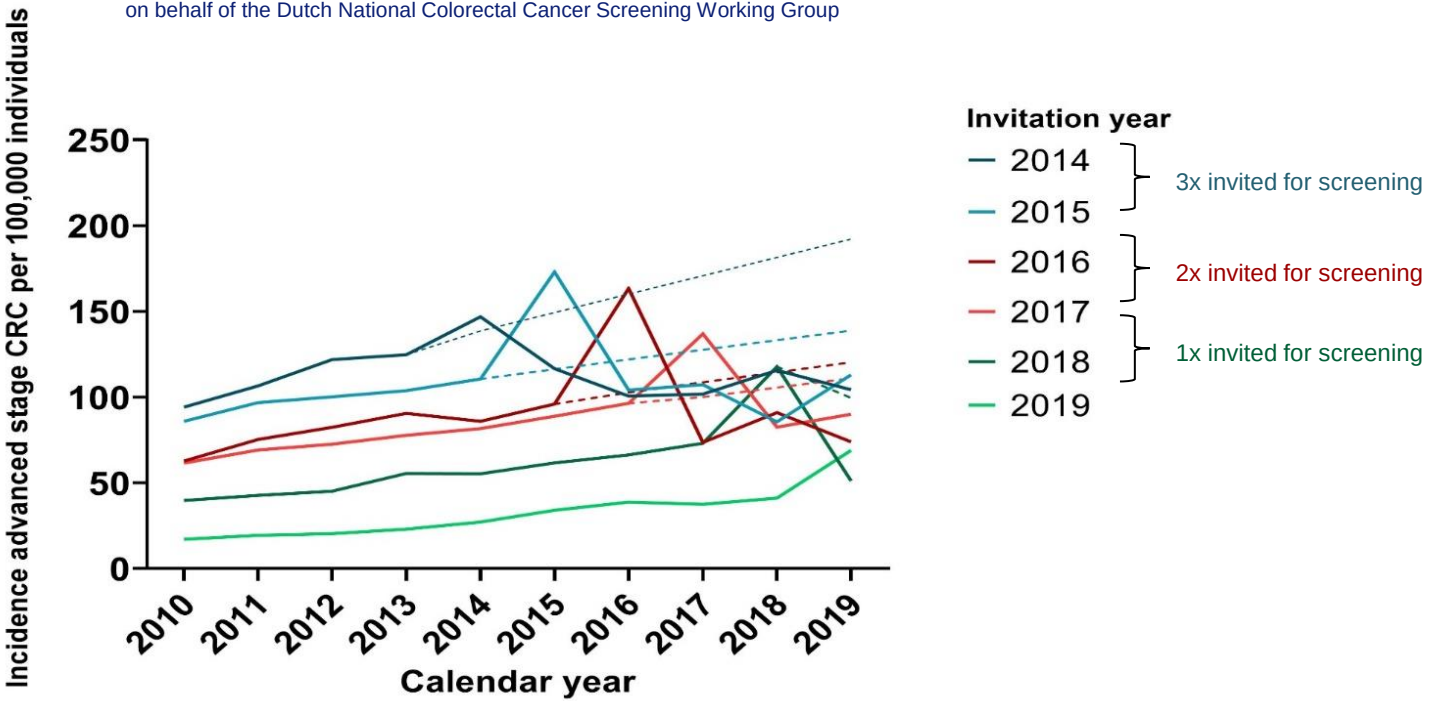
- ↓ CRC incidence
- ↓ incidence advanced-stage CRC
- Improved treatment options

Early indicators of decreased *morbidity* and *mortality* in the long-term, as a result of the introduction of the programme

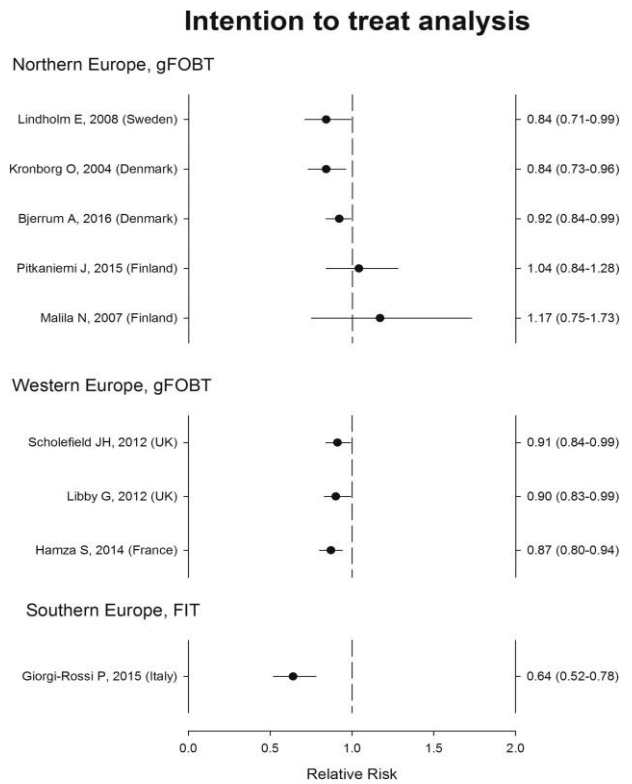
Lancet Gastroenterology & Hepatology, nov 2021

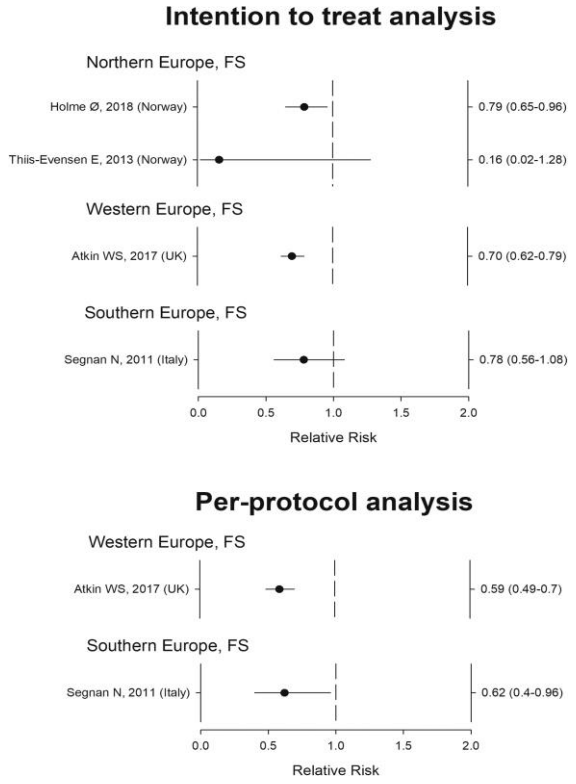
E. C. H. Breekveldt, I. Lansdorp-Vogelaar, E. Toes-Zoutendijk, M. C. W. Spaander, A. J. van Vuuren, F. J. van Kemenade, C. R. B. Ramakers, E. Dekker, I. D. Nagtegaal, M. F. Krul, N. F. M. Kok, K. F. D. Kuhlmann, G. R. Vink, M. E. van Leerdam, M. A. G. Elferink

on behalf of the Dutch National Colorectal Cancer Screening Working Group



Effectiveness colorectal cancer screening





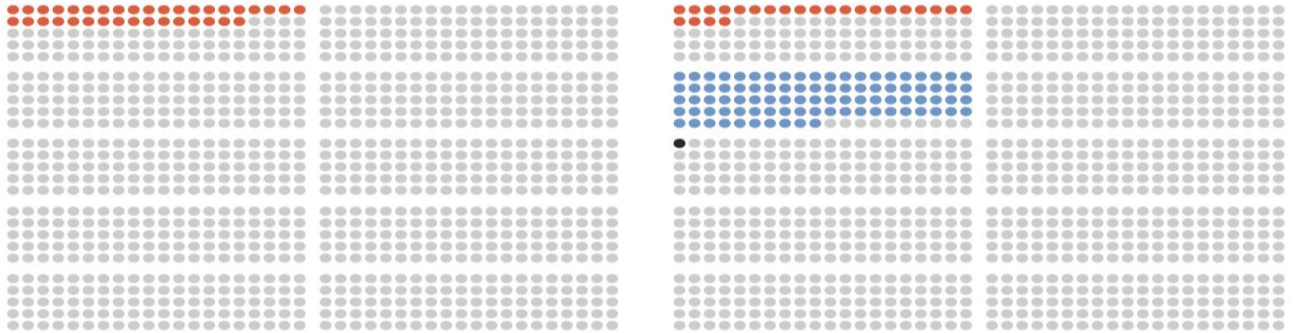
Andrea Gini et al., European Journal of Cancer
Volume 127 Pages 224-235 (March 2020)
DOI: 10.1016/j.ejca.2019.12.014

FIT screening in the Netherlands

Model estimates for women aged 40 years and older who were invited to screening between 55 and 75 years biennally, followed their lifetimes (FIT attendance 74%, colonscopy attendance 79,8%)

1000 women without screening

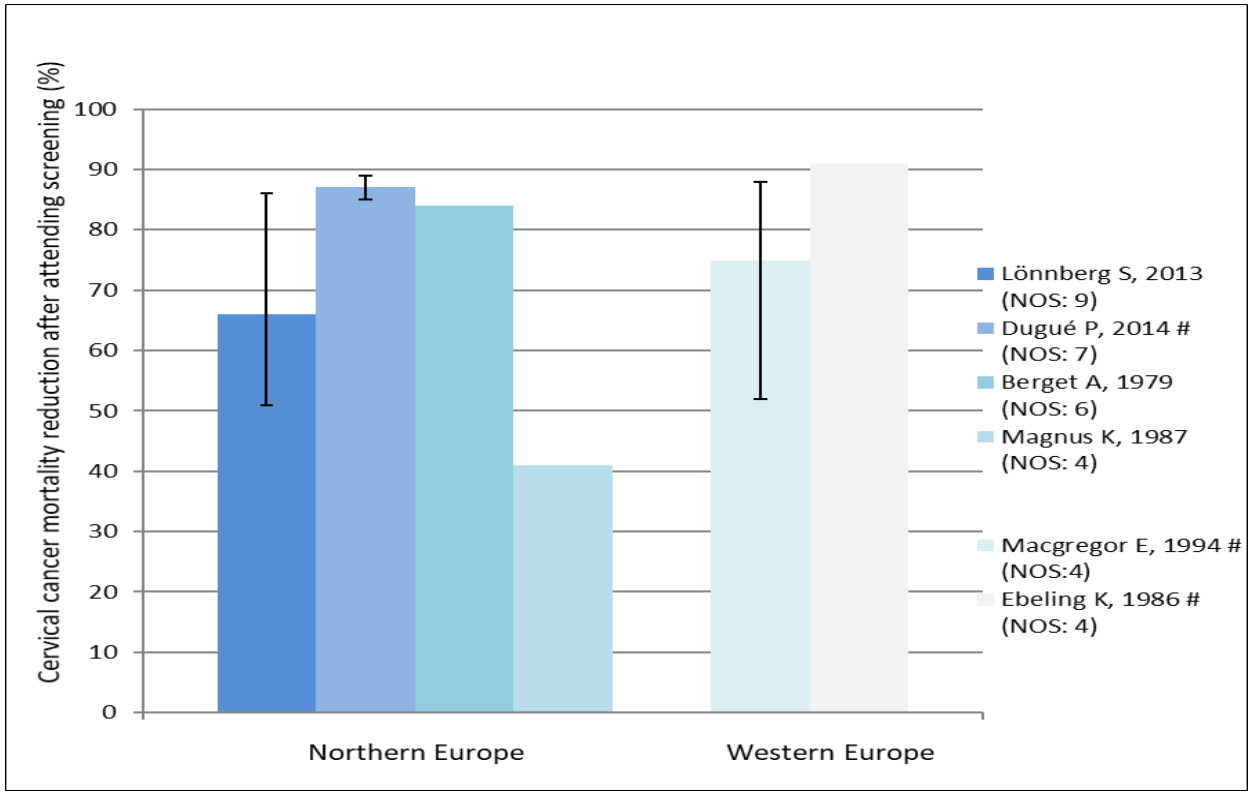
1000 women with screening



	Without screening	With screening
Women who died from CRC cancer	36	24
Women with a false-positive result[1]	-	90
Women who were unnecessarily diagnosed and treated[2]	-	1
Remaining women	964	885

[1] negative colonoscopy or non-advanced adenoma
[2] number of advanced adenomas and cancers

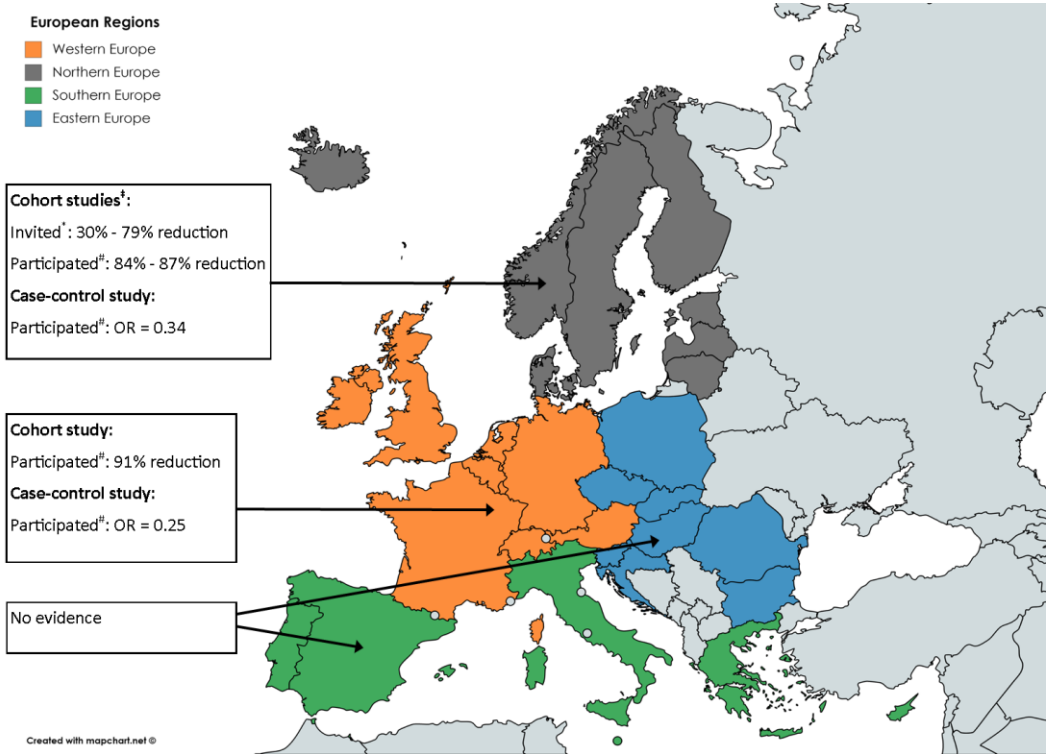
Systematic review: Cervical cancer mortality reduction



NOS = Newcastle Ottawa scale (i.e. a higher score is a lower risk of bias); Confidence intervals are shown as error bars if they were reported in the corresponding study.

Source: Jansen et al. EJC 2020.

Screening effectiveness evidence by European region. Cervical cancer mortality reduction



RR, Relative risk; OR, Odds ratio (ratio between the odds of dying from cervical cancer for each study group); ‡Studies with a high risk of bias were excluded for this figure; *Invited vs. Non-invited women; and #Participating vs. Non-participating women.

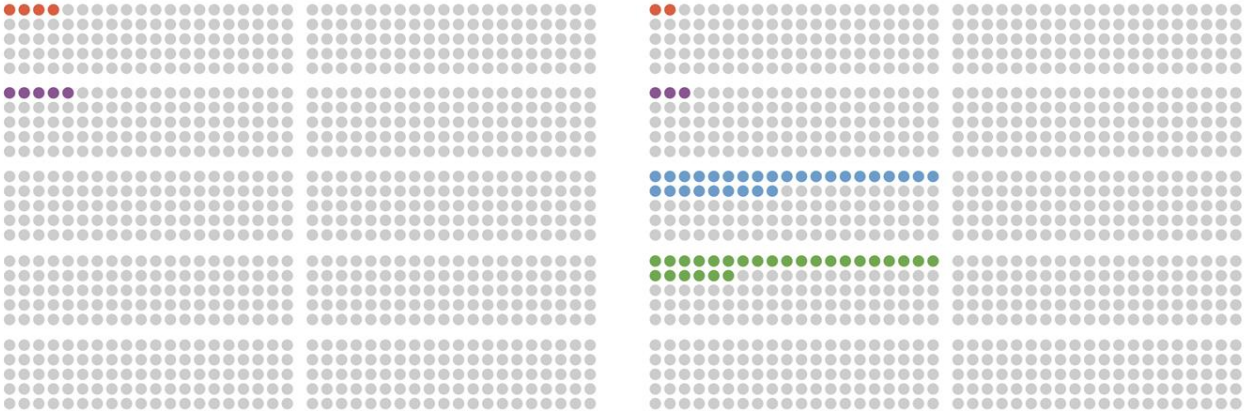
Data source: Jansen et al. EJC 2020

Cervical cancer screening in the Netherlands

Model estimates for women who were invited to screening between 30 and 60 years.

1000 women without screening

1000 women with screening



	Without screening	With screening
Women who died from cervical cancer	4	2
Women with cervical cancer who died from other cause	5	3
Women with a false-positive test result or CIN1 (no treatment)	-	29
Women with CIN2 or CIN3 (treatment)	-	26
Remaining women	991	940

SAPEA

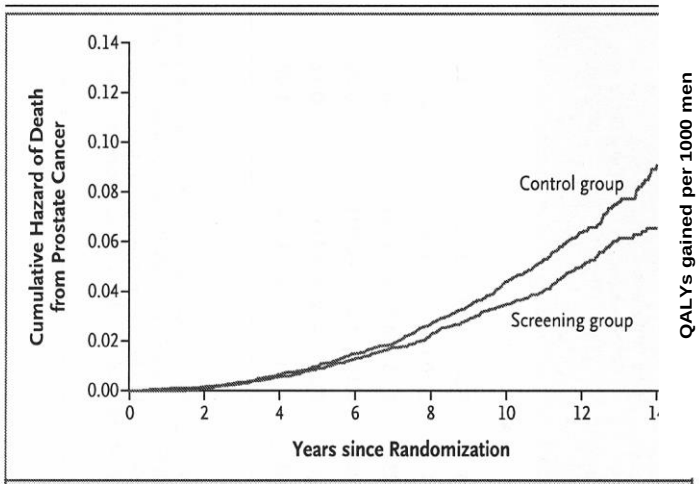
Science Advice for Policy by European Academies

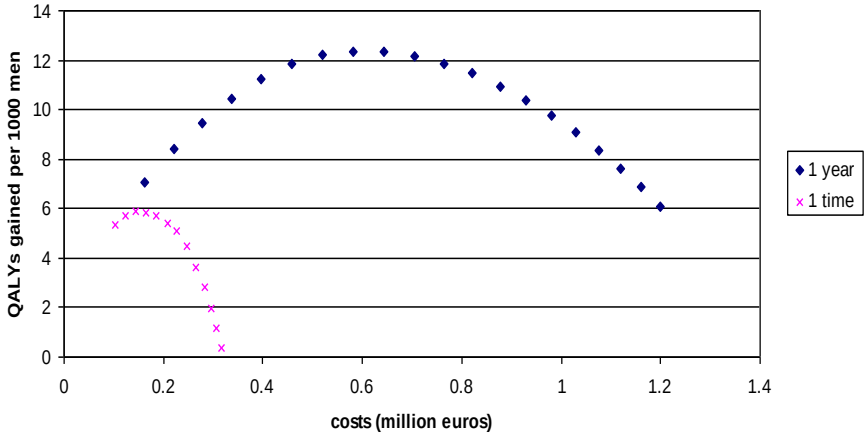
Evidence Review Report No. 10

Should we extend screening programmes?

Prostate cancer

- Prostate cancer is the most commonly diagnosed cancer and the leading cause of cancer death in non-smoking European men





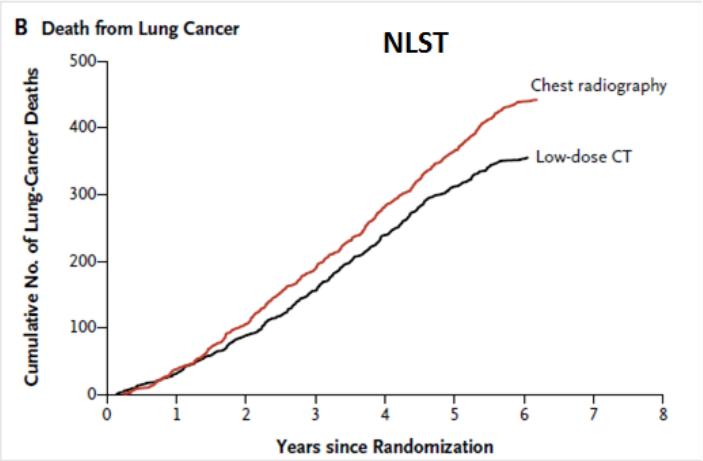
The experts find the scientific basis for organised prostate cancer screening quite strong provided that the age criteria are appropriate. The high levels of opportunistic PSA testing at older ages can lead to overdiagnosis and harm. Likely that MRI (and active surveillance) will become part of prostate screening protocols to further improve net-benefit for individuals.

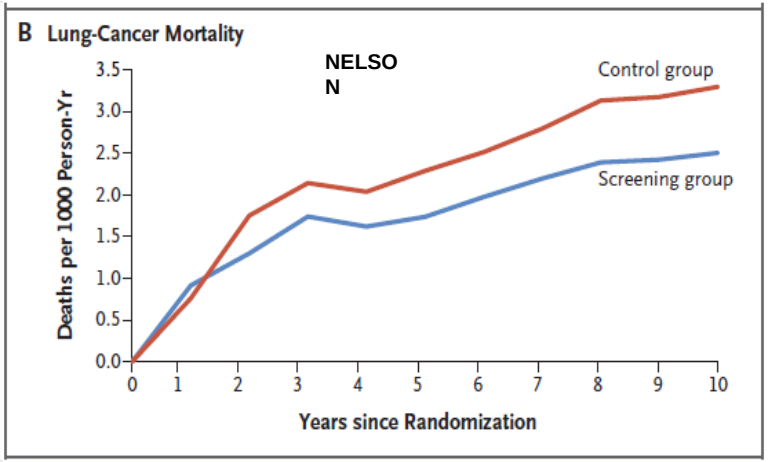
Should we extend screening programmes?

Lung cancer

- High disease burden accounting for 20% cancer deaths in EU

- Two large-scale RCTs show low dose CT scanning (LDCT) reduce cancer mortality for smokers and ex-smokers aged 50 to 80 years





The experts therefore find a strong scientific basis for extending cancer screening programmes in EU to lung cancer screening based on effectiveness and burden

Should we extend screening programmes?

Lung cancer

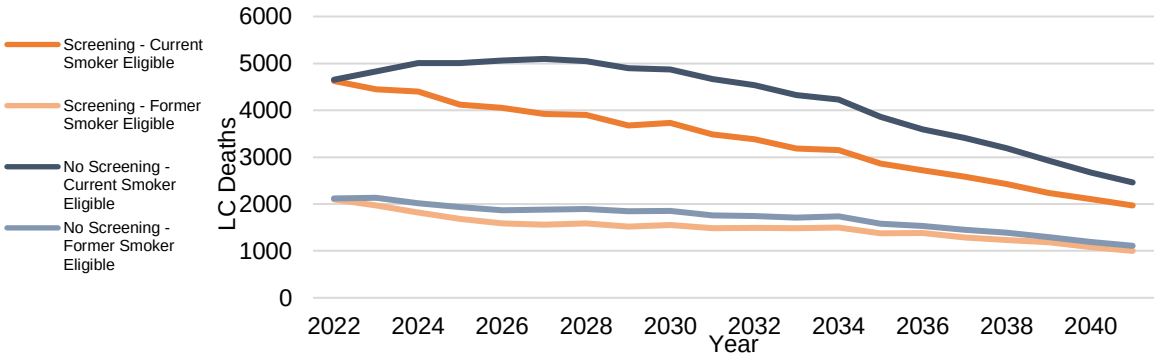
- High disease burden accounting for 20% cancer deaths in EU
- Two large-scale RCTs show low dose CT scanning (LDCT) reduce cancer mortality for smokers and ex-smokers aged 50 to 80 years
- Burden and possible harms of low dose scanning are limited
- Two systematic reviews (12 studies) suggest cost-effective strategies
- US Preventative Service Task Force are recommending LDCT for >50 years at least 20 pack-years and ex-smokers <15 years
- Pilots in UK and some EU countries suggest broad acceptance and provide an opportunity for effective smoking cessation advice

Progress EU

- Croatia 25,000
- Poland 20,000
- The Netherlands 13,000
- RISP Italy 10,000
- Czech 5,000
- Hungary 5,000
- Estonia 4,000

- Norway, Finland, Denmark, *Belgium (Flanders), France, Germany*, Latvia, Lithuania, Romania, Slovakia, Bulgaria, Montenegro, Slovenia.

Predicted LC Outcomes over time



	2022 (Y0)		2030 (Y8)	2035 (Y13)	2040 (Y18)
Ever-Eligible Population	826,365				
<u>Cumulative</u> screens and health outcomes from 2022 onwards		Screens	2.28m	3.24m	3.60m
		Late-Stage LC (III-IV) Reduction	7,888 *(17.0%)*	14,018 *(19.7%)*	19,473 *(20.8%)*
		LC Mortality Reduction	8,330 *(15.1%)*	15,304 *(17.6%)*	20,919 *(18.2%)*

De Nijs et al., eclinmed 2024 (NL 18 million)

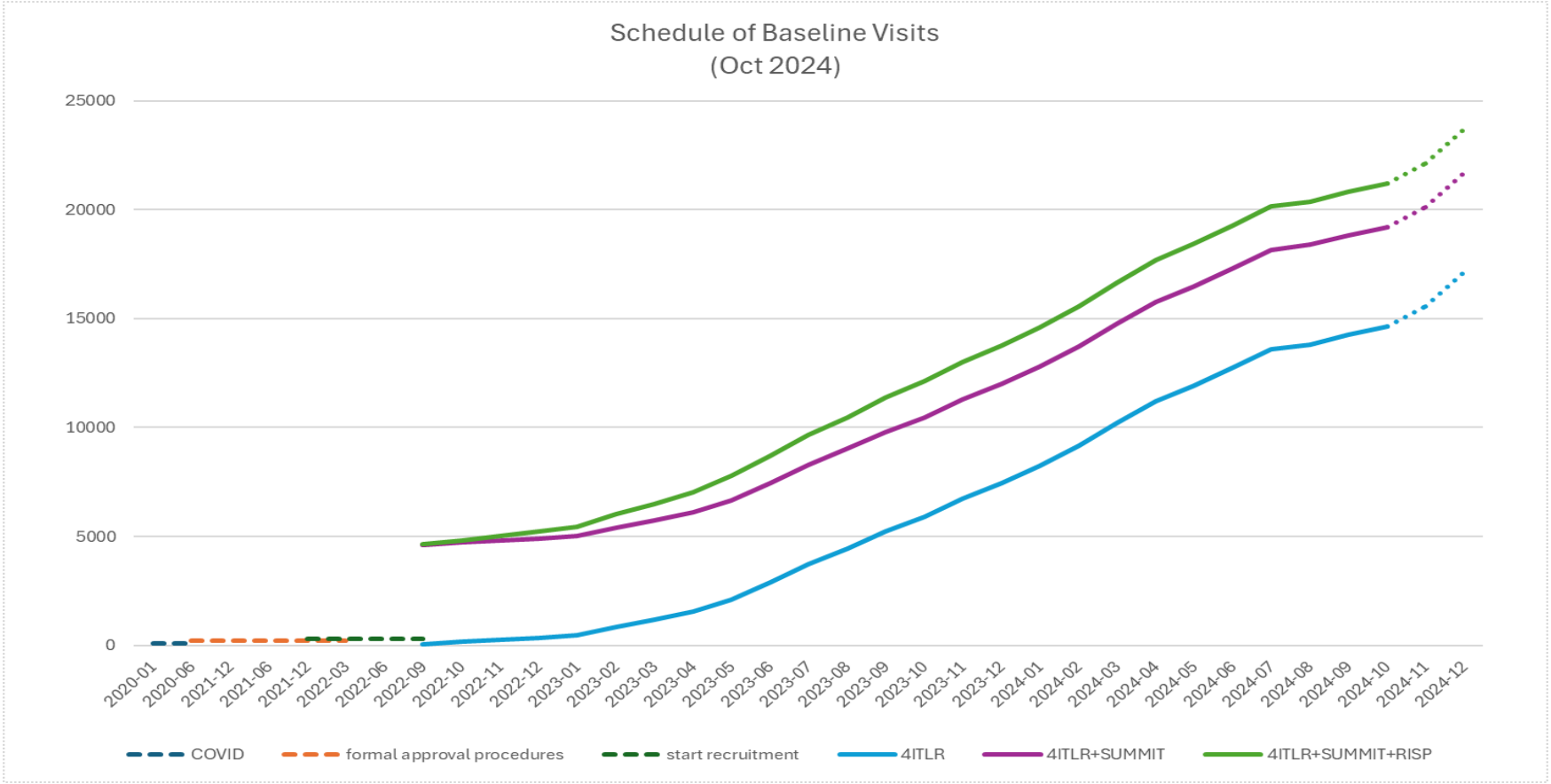
4-IN-THE-LUNG-RUN

This project is co-funded under the HORIZON 2020 Programme under grant agreement no. 848294

- The first large-scale multi-centered implementation trial on Volume CT lung cancer screening across 6 European countries

- To assess the relative safety* of a personalized risk-based (often) less intensive screening regimen amongst high risk individuals#

- * i.e., comparable detection of favourable lung cancer stages I-II
- # individuals aged 60-79 years, with a $PLCO_{m2012}$ 6-jaars LC risk ≥2.6% or a smoking history of
- ≥35 PY, being a current smoker or former smoker who quit smoking ≤10 years ago


Schedule of Baseline Visits
(Oct 2024)
25000
20000
15000
10000
5000
0
2020-01
2020-06
2021-12
2021-06
2021-12
2022-03
2022-06
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2024-03
2024-04
2024-05
2024-06
2024-07
2024-08
2024-09
2024-10
2024-11
2024-12
COVID
formal approval procedures
start recruitment
4ITLR
4ITLR+SUMMIT
4ITLR+SUMMIT+RISP

Triage at Baseline LDCT

Category	Participants			Action
	PanCan	LungRADS	4-ITLR	
Very low risk	**75%**	**-**	**77%****	12-24 months
Low risk	**14%**	**83%**	**-**	12 months
Moderate risk	**8.2%**	**9.8%**	**20%**	3 or 6 months
High risk	**2.8%**	**7.4%**	**2.7%**	Refer

- Following the positive results of the Dutch-Belgian Lung Cancer Screening (NELSON) trial, **4-IN-THE-LUNG-RUN** aims to provide significant evidence and cost savings for both citizens as well as health care systems in Europe for the implementation of personalised lung cancer screening, possibly the first large-scale risk-based cancer screening programme in Europe.
- The goal is to improve health by controlling current and future risks by moving away from a "one-size-fits-all" approach.

Strengthening the screening of Lung Cancer in Europe (SOLACE) project

The SOLACE aim is to ensure implementation and optimisation of effective, advanced state-of-the-art lung cancer screening programmes in Europe.

Participant countries

Austria, Belgium, Croatia, Czechia, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Romania, Spain

PILOTS

Females

- Needs of females
- How to increase participation in LCSPs
- Liaise with breast cancer screening
- Assessed in 10 countries

Hard to reach

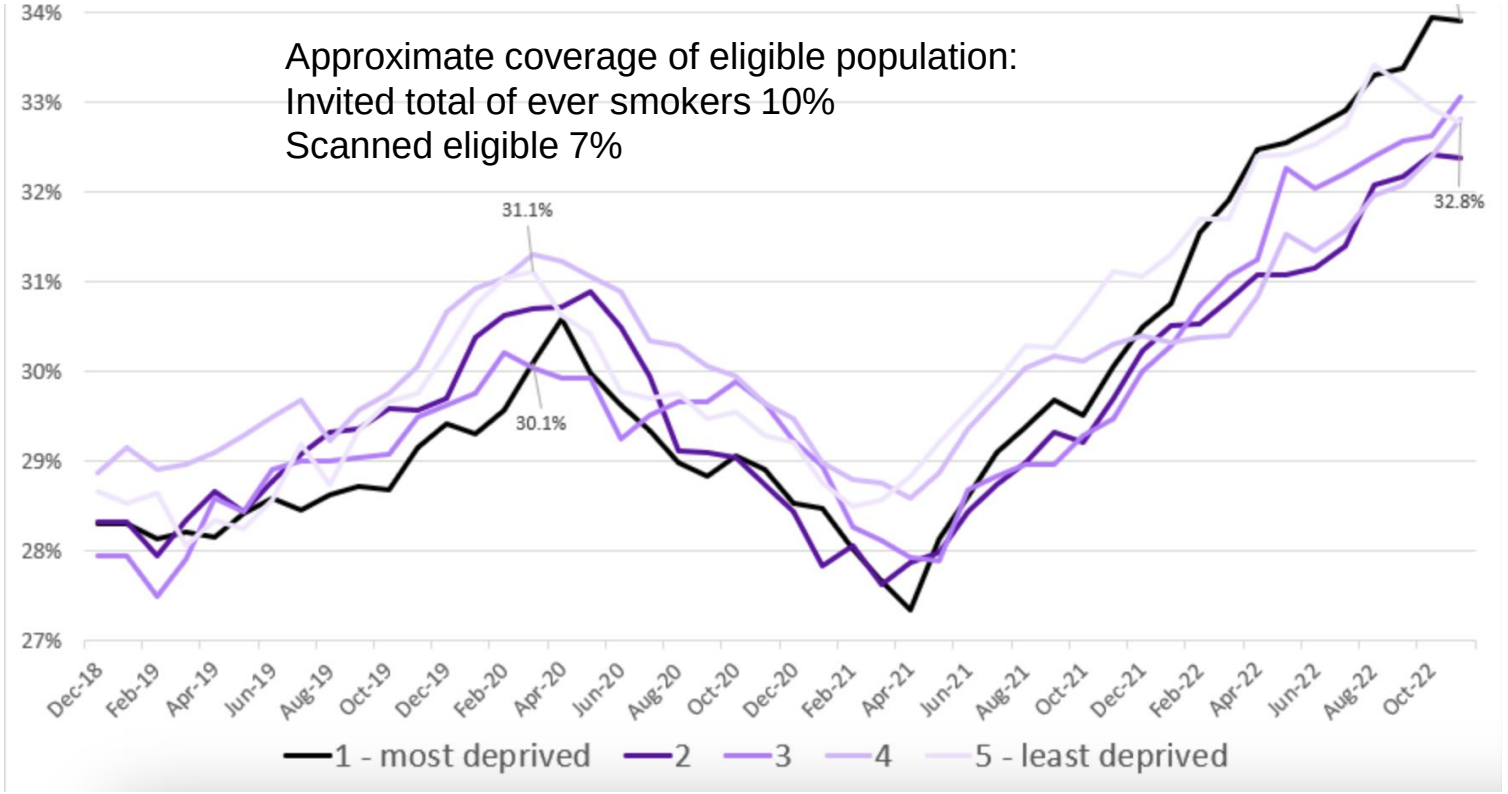
- Needs of marginalised and vulnerable populations
- Addressing language barriers and ethnicity
- Working with trained mediators

Comorbidities

- Special needs of high-risk populations with comorbidities
- Focussing on COPD, interstitial lung disease and cancer survivors

This project is co-funded under the EU4Health Programme 2021–2027 under grant agreement no. 101101187

Impact of TLHC on early stage by deprivation – narrowing the gap



Screen,

But not too much

Screening is likely to reduce socio-economic health disparities !

Risks & benefits of cancer screening programmes

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