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I programmi di screening mammografico in Europa: valutazione degli esiti e primo bilancio benefici/danni

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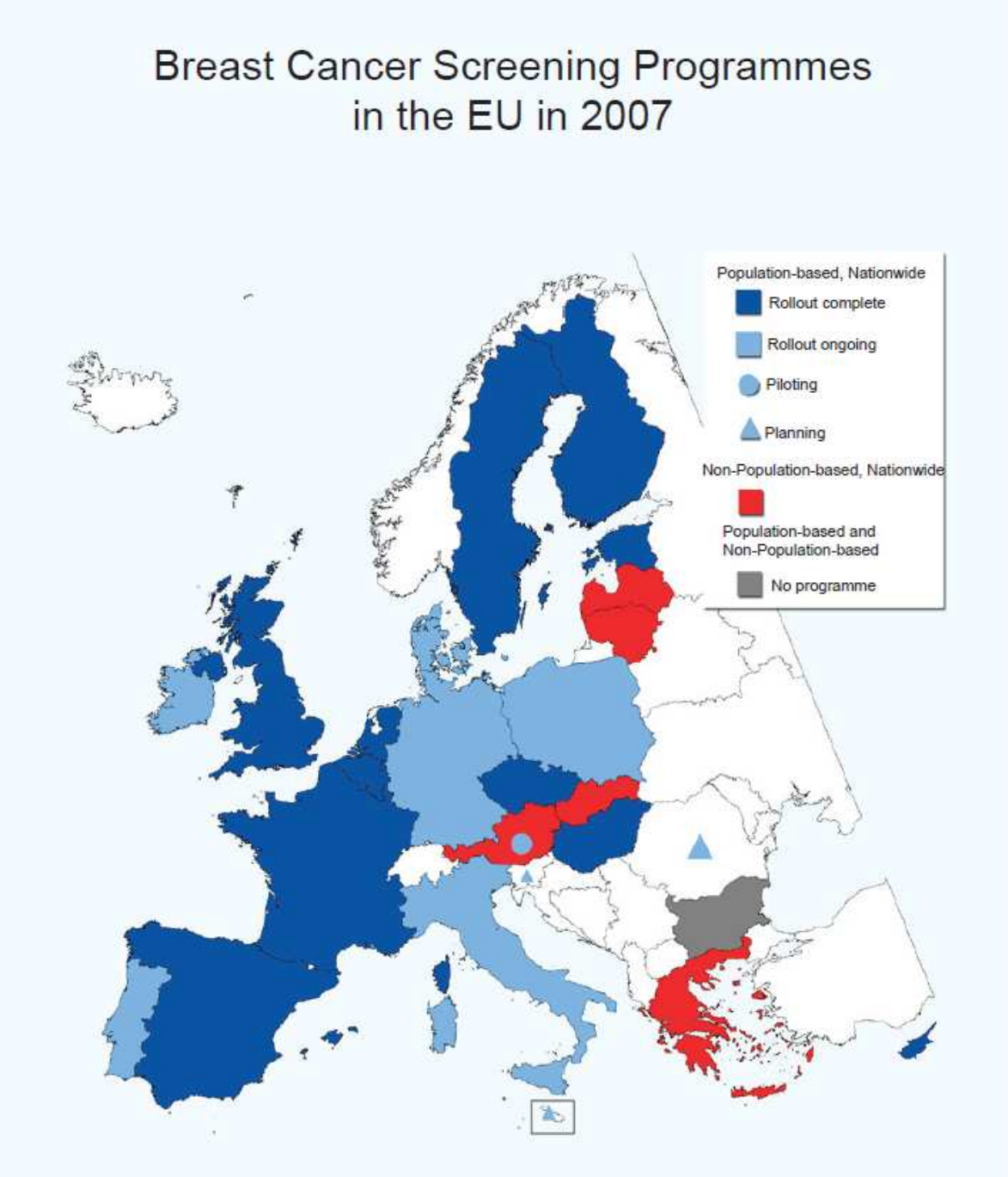
BACKGROUND

- Randomised clinical trials in the 1970s and 1980s
- Population-based screening programmes were implemented in most European countries at the beginning of the 1990s
- In 2007 the total population targeted by a mammographic screening programme comprised 26.9 million women, predominantly aged 50-69.



von Karsa L et al.
Cancer screening in the European Union. Report on the implementation of the council recommendation on cancer screening. First report.
IARC 2008

BACKGROUND

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THE CRITICISMS OF MAMMOGRAPHY SCREENING

- The effectiveness in reducing breast cancer mortality was recently questioned on the basis of two observational studies
  (Jorgensen et al, BMJ 2009; Kalager et al, New Engl J Med 2010)
- The problem of overdiagnosis and other side-effects have been raised by some authors who have tried to quantify them
  (Esserman et al, JAMA 2009; Gotzsche et al, BMJ 2009)

BMJ 2009

Breast screening: the facts— or maybe not

Peter Gøtzsche and colleagues argue that women are still not given enough, or correct, information about the harms of screening

Summary from evidence based leaflet

- It may be reasonable to attend for breast cancer screening with mammography, but it may also be reasonable not to attend because screening has both benefits and harms
- If 2000 women are screened regularly for 10 years, one will benefit from the screening, as she will avoid dying from breast cancer
- At the same time, 10 healthy women will, as a consequence, become cancer patients and will be treated unnecessarily. These women will have either a part of their breast or the whole breast removed, and they will often receive radiotherapy and sometimes chemotherapy
- Furthermore, about 200 healthy women will experience a false alarm. The psychological strain until one knows whether it was cancer, and even afterwards, can be severe

Radiology

Is Mammographic Screening Justifiable Considering Its Substantial Overdiagnosis Rate and Minor Effect on Mortality?

Karsten Juhl Jørgensen, MD
John D. Keen, MD, MBA
Peter C. Gøtzsche, MD

Proponents of mammographic screening generally say that the benefit is large and established beyond doubt, that there is little overdiagnosis, and that screening leads to less invasive treatment (1–3). The truth is that the benefit is doubtful, that overdiagnosis is substantial and certain, and that screening increases the number of mastectomies performed.

EUROSCREEN WORKING GROUP

EUROSCREEN is a cooperative group that includes experts involved in planning and evaluating most of the population-based screening programmes in Europe.

Coordinators:

E. Paci (Italy), M. Broeders (Netherland), S. Hofvind (Norway) and SW Duffy (UK)

Members:

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THE PROJECT

We aimed to present a 'balance sheet' based on estimates of breast cancer mortality reduction as the primary benefit, and overdiagnosis of breast cancer and false-positive screening tests as the most important harms.

Five literature reviews were conducted based on the observational published studies in Europe evaluating:

1) breast cancer mortality reduction (trend studies, incidence-based mortality studies and case-control studies)
2) breast cancer overdiagnosis
3) false-positive results

THE PROJECT

The project was supported by the National Centre for Screening Monitoring (ONS).

The project has started on November 2010 and there were two international meeting in Florence.

The results of this project for the evaluation of service screening in Europe are published in a supplement of the *Journal of Medical Screening* :

Weighing up the benefits and harms of breast cancer service screening in Europe. J Med screen 2012; 19(Suppl1)

ORIGINAL ARTICLE

The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies

Mireille Broeders, Sue Moss, Lennarth Nyström, Sisse Njor, Håkan Jonsson, Ellen Paap, Nathalie Massat, Stephen Duffy, Elsebeth Lynge and Eugenio Paci, for the EUROSCREEN Working Group

J Med Screen 2012;**19 Suppl 1**:14–25
DOI: 10.1258/jms.2012.012078

Objectives To assess the impact of population-based mammographic screening on breast cancer mortality in Europe, considering different methodologies and limitations of the data.

Methods We conducted a systematic literature review of European trend studies ($n = 17$), incidence-based mortality (IBM) studies ($n = 20$) and case-control (CC) studies ($n = 8$). Estimates of the reduction in breast cancer mortality for women invited versus not invited and/or for women screened versus not screened were obtained. The results of IBM studies and CC studies were each pooled using a random effects meta-analysis.

Results Twelve of the 17 trend studies quantified the impact of population-based screening on breast cancer mortality. The estimated breast cancer mortality reductions ranged from 1% to 9% per year in studies reporting an annual percentage change, and from 28% to 36% in those comparing post- and prescreening periods. In the IBM studies, the pooled mortality reduction was 25% (relative risk [RR] 0.75, 95% confidence interval [CI] 0.69–0.81) among invited women and 38% (RR 0.62, 95% CI 0.56–0.69) among those actually screened. The corresponding pooled estimates from the CC studies were 31% (odds ratio [OR] 0.69, 95% CI 0.57–0.83), and 48% (OR 0.52, 95% CI 0.42–0.65) adjusted for self-selection.

Conclusions Valid observational designs are those where sufficient longitudinal individual data are available, directly linking a woman's screening history to her cause of death. From such studies, the best 'European' estimate of breast cancer mortality reduction is 25–31% for women invited for screening, and 38–48% for women actually screened. Much of the current controversy on breast cancer screening is due to the use of inappropriate methodological approaches that are unable to capture the true effect of mammographic screening.

See end of article for authors' affiliations

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We reviewed all the observation studies evaluating the impact of a population-based mammographic screening programme in Europe on breast cancer mortality.

Trend studies (n=17): the analysis of breast cancer mortality trends is not adequate for evaluating the impact of screening

Incidence-based mortality studies (n=20): the pooled estimate of breast cancer mortality reduction from IBM studies was 38% among screened women.

Case-control studies (n=8): the pooled estimate of breast cancer mortality reduction from case-control studies was 48% among screened women, after adjustment for self-selection bias.

ORIGINAL ARTICLE

Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review

Donella Puliti, Stephen W Duffy, Guido Miccinesi, Harry de Koning, Elsebeth Lynge, Marco Zappa, Eugenio Paci and the EUROSCREEN Working Group (members listed at the end of the paper)

J Med Screen 2012;**19 Suppl 1**:42–56
DOI: 10.1258/jms.2012.012082

See end of article for authors' affiliations

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Accepted for publication 21 June 2012

Objectives Overdiagnosis, the detection through screening of a breast cancer that would never have been identified in the lifetime of the woman, is an adverse outcome of screening. We aimed to determine an estimate range for overdiagnosis of breast cancer in European mammographic service screening programmes.

Methods We conducted a literature review of observational studies that provided estimates of breast cancer overdiagnosis in European population-based mammographic screening programmes. Studies were classified according to the presence and the type of adjustment for breast cancer risk (data, model and covariates used), and for lead time (statistical adjustment or compensatory drop). We expressed estimates of overdiagnosis from each study as a percentage of the expected incidence in the absence of screening, even if the variability in the age range of the denominator could not be removed. Estimates including carcinoma *in situ* were considered when available.

Results There were 13 primary studies reporting 16 estimates of overdiagnosis in seven European countries (the Netherlands, Italy, Norway, Sweden, Denmark, UK and Spain). Unadjusted estimates ranged from 0% to 54%. Reported estimates adjusted for breast cancer risk and lead time were 2.8% in the Netherlands, 4.6% and 1.0% in Italy, 7.0% in Denmark and 10% and 3.3% in England and Wales.

Conclusions The most plausible estimates of overdiagnosis range from 1% to 10%. Substantially higher estimates of overdiagnosis reported in the literature are due to the lack of adjustment for breast cancer risk and/or lead time.

Overdiagnosis: "Detection of in situ or invasive breast cancers at screening that would have never clinically surfaced in the absence of screening" (Paci and Duffy, Breast Cancer Research, 2005)

We selected 13 primary studies reporting estimates of breast cancer overdiagnosis in seven European population-based mammographic screening programmes.

Studies were classified according to the presence and the type of adjustment for breast cancer risk and for lead time.

The **most plausible estimates range from 1% to 10%** of the expected incidence in the absence of screening.

The **average estimate** of overdiagnosis in screened women from 50 to 69 years **was 6.5%,** including carcinoma in situ.

ORIGINAL ARTICLE

False-positive results in mammographic screening for breast cancer in Europe: a literature review and survey of service screening programmes

Solveig Hofvind, Antonio Ponti, Julietta Patnick, Nieves Ascunce, Sisse Njor, Mireille Broeders, Livia Giordano, Alfonso Frigerio and Sven Törnberg The EUNICE Project and Euroscreen Working Groups (Members of the EUNICE Project and Euroscreen Working Groups listed at end of paper)

J Med Screen 2012;**19 Suppl 1**:57–66
DOI: 10.1258/jms.2012.012083

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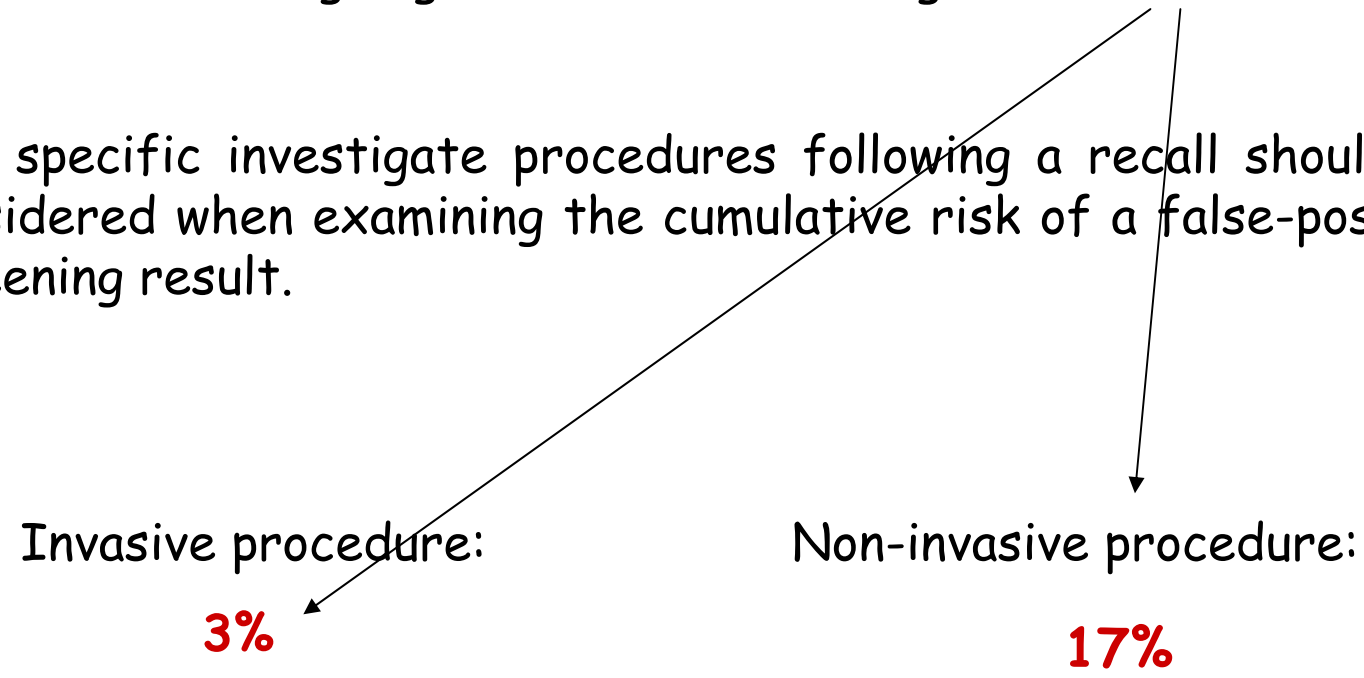
Accepted for publication 22 June 2012

Objective To estimate the cumulative risk of a false-positive screening result in European mammographic screening programmes, and examine the rates and procedures of further assessment.
Methods A literature review was conducted to identify studies of the cumulative risk of a false-positive result in European screening programmes (390,000 women). We then examined aggregate data, cross-sectional information about further assessment procedures among women with positive results in 20 mammographic screening programmes from 17 countries (1.7 million initial screens, 5.9 million subsequent screens), collected by the European Network for Information on Cancer project (EUNICE).
Results The estimated cumulative risk of a false-positive screening result in women aged 50–69 undergoing 10 biennial screening tests varied from 8% to 21% in the three studies examined (pooled estimate 19.7%). The cumulative risk of an invasive procedure with benign outcome ranged from 1.8% to 6.3% (pooled estimate 2.9%). The risk of undergoing surgical intervention with benign outcome was 0.9% (one study only). From the EUNICE project, the proportions of all screening examinations in the programmes resulting in needle biopsy were 2.2% and 1.1% for initial and subsequent screens, respectively, though the rates differed between countries; the corresponding rates of surgical interventions among women without breast cancer were 0.19% and 0.07%.
Conclusion The specific investigative procedures following a recall should be considered when examining the cumulative risk of a false-positive screening result. Most women with a positive screening test undergo a non-invasive assessment procedure. Only a small proportion of recalled women undergo needle biopsy, and even fewer undergo surgical intervention.

A **false-positive screening test** was defined as any screening test requiring further diagnostic assessment in which neither invasive breast cancer nor DCIS was diagnosed.

The **cumulative risk of a false-positive screening** result in women aged 50-69 undergoing 10 biennial screening tests **was 20%**

The specific investigate procedures following a recall should be considered when examining the cumulative risk of a false-positive screening result.



ORIGINAL ARTICLE

Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet

EUROSCREEN Working Group

J Med Screen 2012;**19 Suppl 1**:5–13
DOI: 10.1258/jms.2012.012077

See end of article for authors' affiliations

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Accepted for publication 13 June 2012

Objectives To construct a European 'balance sheet' of key outcomes of population-based mammographic breast cancer screening, to inform policy-makers, stakeholders and invited women.
Methods From the studies reviewed, the primary benefit of screening, breast cancer mortality reduction, was compared with the main harms, over-diagnosis and false-positive screening results (FPRs).
Results Pooled estimates of breast cancer mortality reduction among invited women were 25% in incidence-based mortality studies and 31% in case-control studies (38% and 48% among women actually screened). Estimates of over-diagnosis ranged from 1% to 10% of the expected incidence in the absence of screening. The combined estimate of over-diagnosis for screened women, from European studies correctly adjusted for lead time and underlying trend, was 6.5%. For women undergoing 10 biennial screening tests, the estimated cumulative risk of a FPR followed by non-invasive assessment was 17%, and 3% having an invasive assessment. For every 1000 women screened biennially from age 50–51 until age 68–69 and followed up to age 79, an estimated seven to nine lives are saved, four cases are over-diagnosed, 170 women have at least one recall followed by non-invasive assessment with a negative result and 30 women have at least one recall followed by invasive procedures yielding a negative result.
Conclusions The chance of saving a woman's life by population-based mammographic screening of appropriate quality is greater than that of over-diagnosis. Service screening in Europe achieves a mortality benefit at least as great as the randomized controlled trials. These outcomes should be communicated to women offered service screening in Europe.

Essential components of the decision-making scenario

Components	Value	Comments and communicative implications
Number of women	1000	The average number of women aged 50-51 years in a small city
Age at the start of the risk period (years)	50	Recommended starting age for service screening in Europe
Status in regard to screening	Screened	The outcomes in terms of benefits and harms to screened women are informative to invited women who are making the decision whether or not to attend
Number of screening mammograms expected in the screening period	10 (every 2 years)	Recommended number for service screening in Europe
Age span for screening (years)	50 to 69	Recommended age range for service screening in Europe
Age at the end of follow up (years)	79	The outcomes in terms of benefits and harms refer to the period from 50 to 79 years.

Measure of individual cumulative risk in the absence of screening

Estimation	Parameter	Reference	Comment
Cumulative risk of BC (in situ + invasive) from 50 to 79 years in the absence of screening	6.7%	Cancer Registry 1985-86 (UK, NordCan, Italy)	Based on the age-specific invasive BC incidence rates in the pre-screening period adjusted to include 1 in situ per 20 invasive cancers
Cumulative risk of BC death from 50 to 79 years in the absence of screening	3.0%	Cancer Registry 1985-86 (UK, NordCan, Italy)	Based on the age-specific BC mortality rates in the pre-screening period

Estimates of screening effects

Estimation	Parameter	Reference	Comment
Reduction in BC mortality	38%-48%	Review of IBM studies and case-control studies	Pooled estimates for screened versus unscreened (adjusted for self-selection bias)
Estimate of overdiagnosis (proportion of the incidence in the absence of screening)	1%-10% (average corrected estimate = 6.5%)	Review of overdiagnosis	Range of the six estimates adjusted for BC risk and lead time bias
Cumulative risk of a false positive result with or without invasive assessment	3% and 17%, respectively	Review of false positive results	Estimated for women who participate in all of the 10 expected biennial screening tests

Balance sheet for 1000 women aged 50-51 years, screened biennially until 69 years and followed until 79 years

Balance sheet	
Benefits	**Harms**
7-9 women's lives are saved (out of 30 deaths expected in the absence of screening)	4 women are overdiagnosed (out of 67 cancers expected in the absence of screening)
	170 women have at least one recall with no-invasive assessment giving a negative result
	30 women have at least one recall with invasive assessment giving a negative result

CONCLUSIONS

- Available cumulative evidence from population-based service screening in Europe shows that the chance of a woman's life being saved by mammographic screening is greater than that of being overdiagnosed by screening.

- These results are intended to help a woman who is invited to screening to make an informed personal choice about the possible outcomes and the implications of participating in screening.

Grazie per l'attenzione