

European estimates of the mammography screening balance sheet of benefits and harms: challenges for communication and research

The EUROSREEN Review of Observational Studies

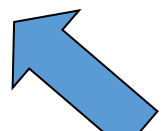
Eugenio Paci , MD, Director , Clinical & Descriptive Epidemiology Unit, Euroscreen Working Group

COUNCIL RECOMMENDATION
of 2 December 2003
on cancer screening
(2003/878/EC)

Screening is, however, testing of healthy people for diseases which have so far not given rise to symptoms. Aside from its beneficial effect on the disease specific mortality or incidence, screening might therefore also have some negative side effects for the screened population.

Health care providers should know all the potential benefits and risks of screening for a given cancer site before embarking on new cancer screening programmes. For the informed public of today, it is furthermore necessary to present these benefits and risks in a way which allows the individual citizen to decide on participation in the screening programmes for her or himself.

The purpose of this document is to give recommendations on cancer screening in the European Union. These recommendations address the people, the politicians and the health administrations of the Member States, the European Commission and the European Parliament



EUROSCREEN WORKING GROUP (2010-2012)

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

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The project was supported by the Italian Screening Monitoring.

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

Journal of Medical Screening

Guest Editors: Allan Hackshaw and Stephen Duffy

Review co-ordinators: E Paci, M Broeders, S Hofvind and SW Duffy

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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;00:1–9
DOI: 10.1258/jms.2012.012077

ORIGINAL ARTICLE

Communicating the balance sheet in breast cancer screening

Livia Giordano, Carla Cogo, Julietta Patnick, Eugenio Paci and the Euroscreen Working Group (members listed at the end of the paper)

J Med Screen 2012;00:1–5
DOI: 10.1258/jms.2012.012084



Benefit: breast cancer mortality reduction

- Trends
- Incidence-based Mortality
- Case control study

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

Incidence –Based Mortality (IBM) studies

Including only BC deaths occurring in women with BC diagnosed *after* their first invitation to screening

- *Intention-to-treat* (ITT) analysis: comparing women *invited to not invited* - based on invitation to avoid selection bias
- *Analysis by attendance*: comparing women *screened with not screened* - correcting for self selection bias

ORIGINAL ARTICLE

Breast cancer mortality in mammographic screening in Europe: a review of incidence-based mortality studies

Sisse Njor, Lennarth Nyström, Sue Moss, Eugenio Paci, Mireille Broeders, Nereo Segnan, Elsebeth Lynge and The Euroscreen Working Group (members listed at the end of the paper)

IBM: the problem of comparison group and estimate of underlying trend

Time period	Screening areas	Non screening areas
Before screening period	Historical control group I	Historical regional control group II
Screening period	STUDY GROUP	Regional control group III

ORIGINAL ARTICLE

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IBM studies

Critical issue :

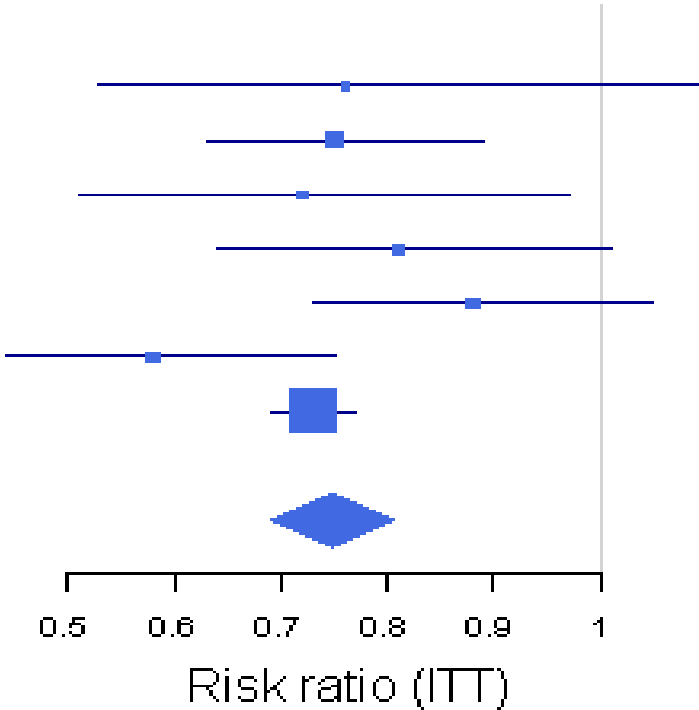
- Have **individual data** directly linking a woman's screening history to her cause of death
- Have **sufficient follow-up** because one needs long term observation to see the benefit in terms of reduced mortality

IBM studies: *women invited vs not invited*

25% reduction

Study	RR	Lower	Upper
Hakama 1997	0.76	0.53	1.09
Olsen 2005	0.75	0.63	0.89
Sarkeala 2008	0.72	0.51	0.97
Paci 2002	0.81	0.64	1.01
Kalager 2010	0.88	0.73	1.05
Ascunce 2007	0.58	0.44	0.75
SOSSEG 2006	0.73	0.69	0.77

Summary (Random) 0.75 0.69 0.81



ORIGINAL ARTICLE

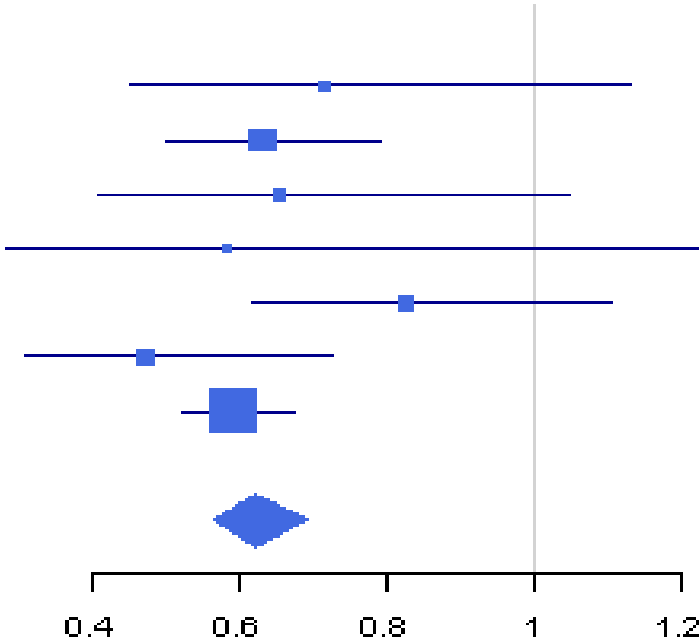
The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies

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

IBM studies:
women screened vs not screened (adjustment for selection (Duffy, 2002)

38% reduction

Study	RR	Lower	Upper
Hakama 1997	0.71	0.45	1.13
Olsen 2005	0.63	0.5	0.79
Sarkeala 2008	0.65	0.41	1.05
Paci 2002	0.58	0.28	1.22
Kalager 2010	0.82	0.62	1.1
Ascunce 2007	0.47	0.31	0.73
SOSSEG 2006	0.59	0.52	0.67
Summary (Random)	0.62	0.56	0.69



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 EUROSREEN Working Group

Case-control studies

A traditional design to assess effectiveness

ORIGINAL ARTICLE

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Design Challenges in screening CC

- **Selection of controls – at risk for BC death, opportunity for screening (time at diagnosis), mostly matched**
- **Screening history before diagnosis of case**
 - *ever* vs. *never* screened
 - *screened* in the period just before diagnosis of the case vs. *not screened* in this period
- **Bias, in particular due to self-selection – women screened vs. not screened**

Case Control studies: a traditional tool to assess screening effectiveness

Original article

Mammographic screening: case-control studies

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Annals of Oncology 14: 1190–1192, 2003
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Overview of the Epidemiology Methods and Applications: Strengths and Limitations of Observational Study Designs

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REJOINDER

Authors' Response, Part I: Observational Studies Analyzed Like Randomized Experiments

Best of Both Worlds

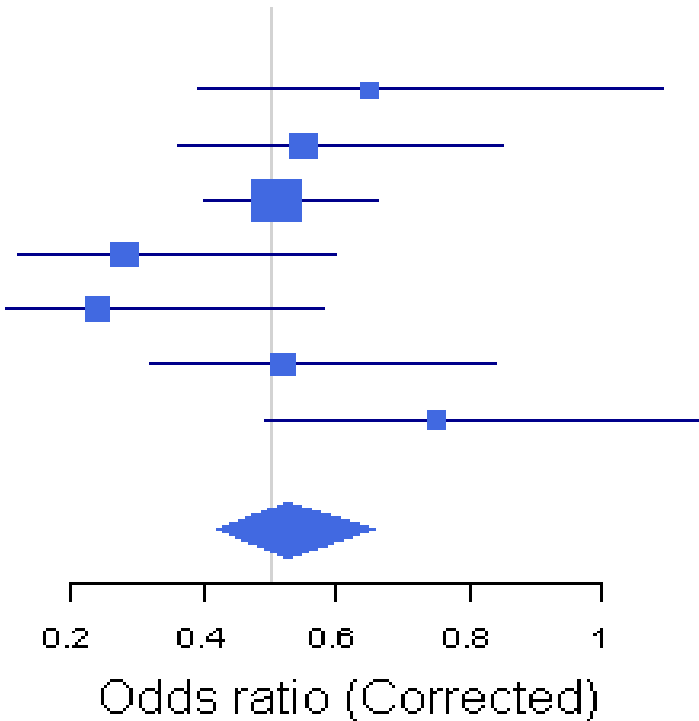
Miguel A. Hernán^a and James M. Robins^b

Epidemiology • Volume 19, Number 6, November 2008

CC-studies: *women screened vs not screened*

48% reduction


Study	OR	Lower	Upper
Gabe 2007	0.65	0.39	1.09
Puliti 2008	0.55	0.36	0.85
Otto 2011	0.51	0.4	0.66
Van Schoor 2011	0.28	0.12	0.6
Paap 2010	0.24	0.1	0.58
Allgood 2008	0.52	0.32	0.84
Fielder 2004	0.75	0.49	1.14
Summary (Random)	0.52	0.42	0.65



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

	UK Independent Review, 2012	EUROSCREEN Working Group (2012)	
Status in regard to screening	Invited	Invited	Screened
Measure of mortality reduction (data source)	20% (randomised controlled trials)	25% - 31% (European observational studies)	38% - 48% (European observational studies)
			

Breast Cancer Mortality Reduction: conclusion

- **The evaluation of the breast cancer mortality reduction in European observational studies confirmed the evidence of efficacy of RCTs**
- **Methodological issues are important in observational study epidemiology, in particular in terms of comparability of population and /or self selection correction (f.ex SES)**
- **Screening is a necessary determinant of the diagnosis of breast cancer (screen detection). Dilution of the analysis with breast cancer cases who had not the opportunity to be screened should be accounted for in study design (IBM for invited or screened)**
- **There are 15-20 years of time difference between RCTs and observational studies of service screening programs**
- **RCTs varied in study design and screening protocol, the same (may be less) for observational screening studies in Europe**

Balance of Benefits and Harms

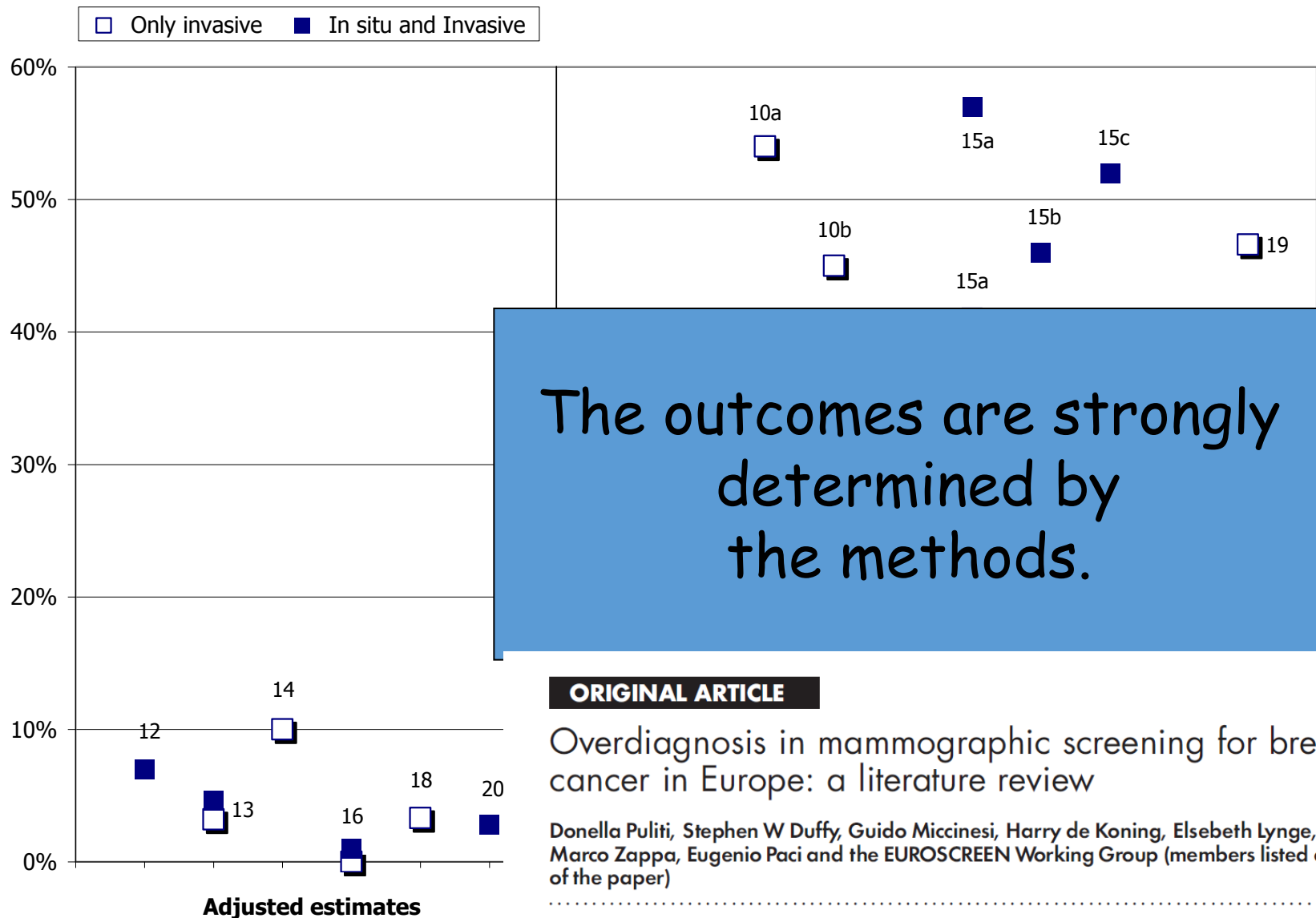
- **Service screening outcomes** should be evaluated in terms of benefits and adverse effects
 - Overdiagnosis is the most important adverse effect
 - Overdiagnosis is usually defined as the proportion of confirmed cancer cases (invasive and in situ) diagnosed during a screening episode that would not have come to clinical attention if screening had not taken place (Paci&Duffy,BCR,2005)

OVERDIAGNOSIS IN BREAST CANCER SCREENING: A REVIEW OF THE EUROPEAN STUDIES

Research articles that gave an original estimate of breast cancer overdiagnosis in population-based mammographic screening programmes in Europe were eligible for inclusion in this review.

Paper	Adjustment for temporal trend	Adjustment for lead time	Estimate of overdiagnosis
Peeters, 1989	Not necessary	No	11.0%
Paci, 2004	No	Statistical adjustment	5.0%
Zahl, 2004	No	No	45%-54%
Jonsson, 2005	No	Statistical adjustment	0-54%
Olsen, 2006	Not necessary	Statistical adjustment	7.0%
Paci, 2006	Yes	Statistical adjustment	4.6%
Waller, 2007	Yes	Compensatory drop	10.0%
Jorgensen, 2009	Yes	No	31% - 41%
Puliti, 2009	Yes	Compensatory drop	1.0%
Jorgensen, 2009	No	Compensatory drop	33.0%
Duffy, 2010	Yes	Compensatory drop	3.3%
Martinez-Alonso, 2010	No	Statistical adjustment	0.4% - 46.6%
de Gelder, 2011	Yes	Compensatory drop	2.8%

OVERDIAGNOSIS ESTIMATES CLASSIFIED ACCORDING TO THE PRESENCE/ABSENCE OF BOTH THE ADJUSTMENTS



Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends

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doi:10.1136/bmj.b2587

ABSTRACT

Objective To estimate the extent of overdiagnosis (the detection of cancers that will not cause death or symptoms) in publicly organised screening programmes.

Design Systematic review of the incidence of breast cancer before and after the introduction of screening programmes. Data sources searched by the authors.

Review methods We searched for studies of breast cancer incidence in women aged 50 years and older, which were controlled for confounding by linear regression. Incidence before and after screening was used to estimate the extent of overdiagnosis.

Results Incidence of breast cancer before screening was fully independent of non-screened women in the United Kingdom; Manitoba, Canada; Australia; Sweden; and Norway. Implementation of screening programmes excluded and incidence and incidence and older, previously estimated at 1.57 (1.53 to 1.61) in England and Wales, 1.44 (1.25 to 1.65) in Manitoba, Canada, 1.53 (1.44 to 1.63) in New South Wales, Australia, 1.46 (1.40 to 1.52) in Sweden, and 1.52 (1.36 to 1.70) in Norway. Overall, the incidence of breast cancer was 1.52 (1.46 to 1.58) in publicly organised screening programmes. One in three breast cancers detected in publicly organised screening programmes was overdiagnosis.

cancers, which would not have been identified clinically in someone's remaining lifetime, is called overdiagnosis and can only be harmful to those who experience it.¹ As it is not possible to distinguish

Geographical area

Rate ratio
(random) (95% CI)

Rate ratio
(random) (95% CI)

England and Wales

1.57 (1.53 to 1.61)

Manitoba, Canada

1.44 (1.25 to 1.65)

New South Wales, Australia

1.53 (1.44 to 1.63)

Sweden

1.46 (1.40 to 1.52)

Norway

1.52 (1.36 to 1.70)

Overall

1.52 (1.46 to 1.58)

Heterogeneity: $I^2=59.0\%$

0.5 1 2

Fig 8| Meta-analysis of overdiagnosis of breast cancer (including carcinoma in situ) in publicly available mammography screening programmes

A distinction must be done between:

incidence excess due to lead time, **needed** for screening efficacy in reducing breast cancer mortality

versus

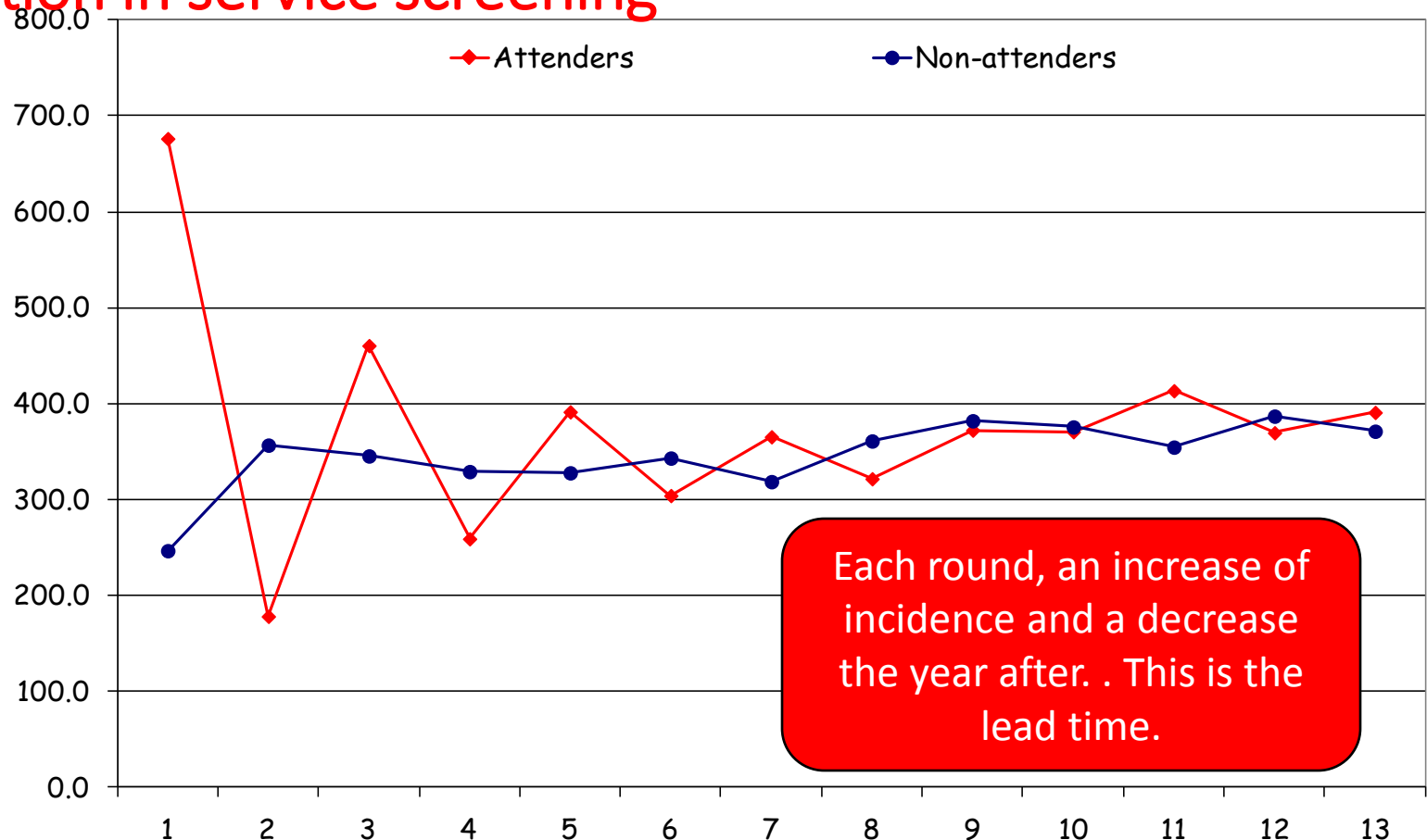
overdiagnosis, i.e. the detection of cancers at screening that would never have clinically surfaced in the absence of screening

Can we disentangle and quantify these two components?

400.000 women cohort, Italy

Invited in service screening and followed up after first invitation, by attendance status (50-69 years old at first invitation). Unpublished data.

Breast cancer incidence by year of follow up since first invitation in service screening



Preliminary data, non published

OBSERVATIONAL STUDIES

Review

Effects of study methods and biases on estimates of invasive breast cancer overdetected with mammography screening: a systematic review

Corné Biesheuvel, Alexandra Barratt, Kirsten Howard, Nehmat Houssami, Les Irwig

“The theoretically most robust method to estimate overdetected is the **cumulative-incidence approach with data from a randomised controlled trial, in which there is more than several years of follow-up after screening stops, and the control group is never screened.”**

“If there is little or no follow-up after the last screen, there will be lead-time bias that should be adjusted for statistical methods, otherwise the estimate of overdetected will be too high.” **(adjusted for lead-time method)**

Lancet oncology, 2007

ADJUSTMENT FOR BREAST CANCER RISK

A valid comparison group should include women with comparable age range and with an underlying BC risk similar to the screened population.

- **When the incidence of the unscreened population is derived from the pre-screening period, an adjustment for the temporal trend is needed.**
- **When the incidence of the unscreened population is derived from a contemporaneous not screened area, an adjustment for pre-screening geographical differences is needed.**

ADJUSTMENT FOR LEAD TIME

We distinguish two methods to adjust for lead time:

Compensatory drop method (follow up of the cohort)

In the absence of OD, the initial increase in BC incidence in the screened age groups will be fully compensated by a similar decrease among older age groups were no longer offered screening.

This method requires that a substantial number of women have actually had the opportunity to be screened and have a sufficient follow-up after the screening stops.

Statistical adjustment

If there is a short or no follow-up after the last screen, there will be a lead time bias that should be adjusted for with statistical methods.

Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study

Sophia Zackrisson, Ingvar Andersson, Lars Janzon, Jonas Manjer, Jens Peter Garne

Cohort 1908-22, age 55-69, at 15 years after the end of the screening period (no screening of the control group)

Screening period + 32% (1.14 to 1.53)

Follow up period - 8% (0.79 to 1.06)

**Overdiagnosis
estimate +10% (1.01 to 1.18)**

- **In period 2 a non statistical significant decrease of incidence in the older cohort**

Measure B : 10.7%

Measure C: 19%

Questa seconda misura usa un differente denominatore, ma utilizza gli stessi dati

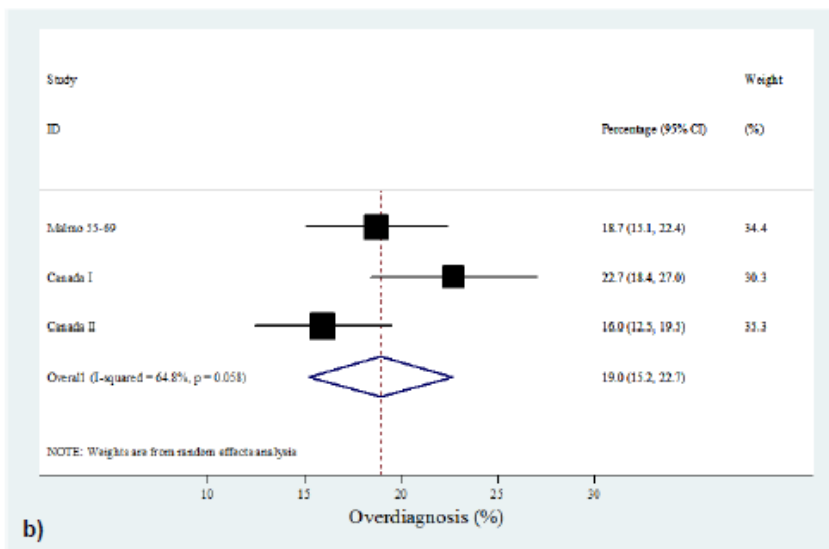
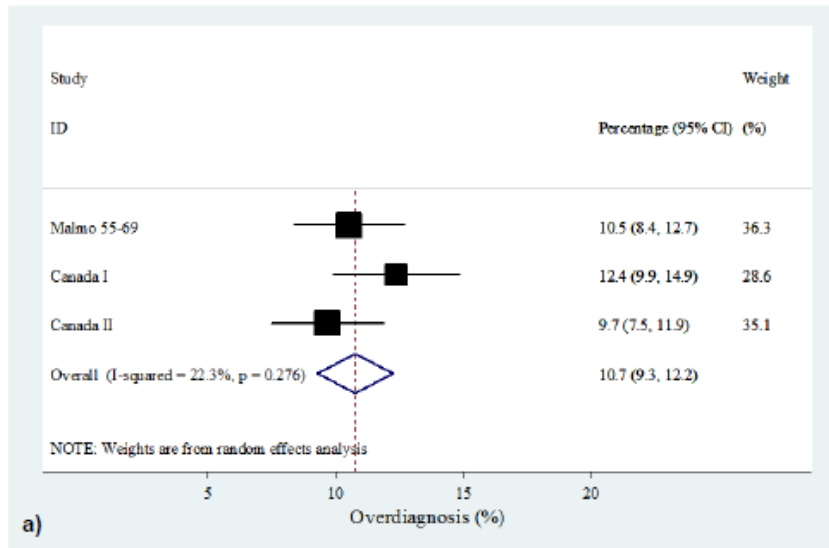


Figure 4.3 Meta-analysis of estimates of overdiagnosis: (a) excess cancers as a proportion of cancers diagnosed over whole follow up period in women invited for screening, (b): excess cancers as a proportion of cancers diagnosed during screening period in women invited for screening

What is the best measure?

The Benefits and Harms of Breast Cancer Screening:

An Independent Review

Lancet , 2012

- A. Excess cancers as a proportion of cancers diagnosed over whole follow up period in unscreened women
- B. Excess cancers as a proportion of cancers diagnosed over whole follow up period in women invited for screening
- C. Excess cancers as a proportion of cancers diagnosed during screening period in women invited for screening
- D. Excess cancers as a proportion of cancers detected at screening in women invited for screening

Measure A is the traditional measure used in the Malmo Trial, and in reviews as Jorgensen, 2009 and EUROSCREEN , 2012

SELECTED STUDIES We included 13 primary studies in our review, reporting 16 estimates of BC overdiagnosis in service screening in seven European countries (The Netherland, Italy, Norway, Sweden, United Kingdom and Spain).

Paper	Adjustment for temporal trend	Adjustment for lead time	Estimate of overdiagnosis
Peeters, 1989	Not necessary	No	11.0%
Paci, 2004	No	Statistical adjustment	5.0%
Zahl, 2004	No	No	45%-54%
Jonsson, 2005	No	Statistical adjustment	0-54%
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Puliti, 2009	Yes	Compensatory drop	1.0%
Jorgensen, 2009	No	Compensatory drop	33.0%
Duffy, 2010	Yes	Compensatory drop	3.3%
Martinez-Alonso, 2010	No	Statistical adjustment	0.4% - 46.6%
de Gelder, 2011	Yes	Compensatory drop	2.8%

Six selected estimates adjusted for the major sources of variability:

Table 3 Population, age range and cancer referred to of the six most reliable estimates of over-diagnosis, with unadjusted and adjusted over-diagnosis estimates

Study	Population	Age range	Cancers	Estimated excess due to over-diagnosis	Adjusted estimates*
Olsen <i>et al.</i> ²⁶	Screened	Screening ages	Invasive + <i>in situ</i>	7.0%	4.4%
Paci <i>et al.</i> ²⁷	Invited	Screening ages	Invasive + <i>in situ</i>	4.6%	5.9%
Waller <i>et al.</i> ²⁸	Screened	Lifetime	Invasive	10.0%	17.0%
Puliti <i>et al.</i> ²⁵	Invited	Screening ages and older	Invasive + <i>in situ</i>	1.0%	1.0%
Duffy <i>et al.</i> ²⁹	Invited	Screening ages	Invasive	3.3%	4.3%
de Gelder <i>et al.</i> ³⁰	Invited	Lifetime	Invasive + <i>in situ</i>	2.8%	6.3%

*Adjusted to apply to screened women, to 50–79 ages and to include carcinoma *in situ*

average estimate = 6.5%

This is the summary measure for overdiagnosis in screened women between 50 and 79 years, including, carcinoma in situ, based on the studies which adequately adjusted for underlying risk and lead time.

THE AVERAGE ESTIMATE FOR THE BALANCE SHEET

The variability in overdiagnosis estimates can also partly be explained by other sources of variability as:

1) Application to screening or invitation:

Note that 4 out of 6 estimates considered pertain to the screening target population (not to women actually screened), so strongly depend on compliance.

2) Application to different age range:

Some studies estimated lifetime overdiagnosis, some overdiagnosis in the screening age range and some in the screening ages and older.

3) Inclusion of all cancers (invasive and in situ) or in situ only

Note that 2 of 6 estimates considered pertain to invasive cancers only.

Major critical points

- **Methodology is different between studies, overdiagnosis estimate is complex and there is no agreed methodology**
- **The use of a cohort approach (the best option) is still rare and limited to older age groups**
- **Most of the studies are statistically adjusted for lead time (different methodology and assumptions)**
- **Studies with high level of the overdiagnosis estimates typically do not adjust for lead time and /or underlying risk (excess of incidence versus overdiagnosis)**

ORIGINAL ARTICLE

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EUROSCREEN Working Group

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See end of article for
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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.

	UK Independent Review, 2012	EUROSCREEN Working Group (2012)	
Status in regard to screening	Invited	Screened	Invited
Measure of Breast cancer mortality reduction (data source)	20% (randomised controlled trials)	38% - 48% (European observational studies)	25% - 31% (European observational studies)
Measure of overdiagnosis (data source)	11-19% * (randomised controlled trials)	6.5% (European observational studies)	4.7% (European observational studies)

***UK PANEL MEASURE B AND C**

P

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.

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

Balance sheet

Benefits

7-9 women's lives are saved
(out of 30 deaths expected
in the absence of screening)

Harms

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

Comparison of the balance sheets of the EUROSCREEN Working group and UK Independent Review (Modified)

	EUROSCREEN Working Group 2012		UK Independent Review, 2012
Status in regard to screening	Screened	Invited	Invited
Expected preventable BC deaths from 50 to 79 years , breast cancer diagnosed in ages 50 -69	19 out 30	19 out 30	19 out 30
N° lives saved	7-9	5-6	4
Expected BC cases from 50 to 79 years	67	67	67
N° overdiagnosed cases	4	3	7- 13 *
N° overdiagnosed cases for every life saved	0.4 – 0.6	0.5 – 0.6	3

***Measure of overdiagnosis estimated using screening period incident breast cancer cases in the Malmo trial. Preliminary, unpublished**

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

10 years

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 woman will avoid dying from breast cancer.
- At the same time, 10 healthy women will be treated unnecessarily. The breast removed, and they will often experience psychological strain.
- 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.

0.5 life saved per 1000 screened women

5 overdiagnosed breast cancer cases per 1000

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Sorting Through the Arguments
on Breast Screening
Michael G. Marmot

- It is doubtful, however, that the independent panel changed the minds of the principal proscreening and antiscreeing groups in the debate over screening. Positions are too entrenched. But the evidence on breast screening is more extensive than in many other areas relevant to population health. If this is not enough for an independent group, coming fresh to the debate, to reach a reasonable judgment, then evidence-based policy is a good deal more difficult than many would believe.

