- **Breast cancer screening Outcome Research**

Red de Programas de Cribado de Cáncer

- **The screening mammography balance of benefits and adverse effects: results based on service screening in Europe**

XV Reunión anual
PAMPLONA
20/21/22 junio

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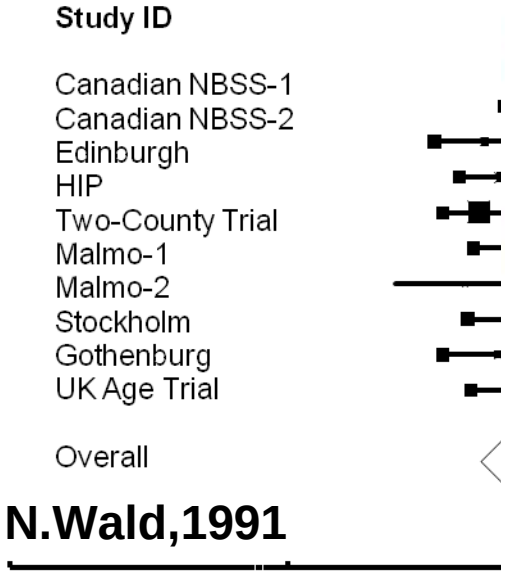

ITALIAN MONITORING CENTRE (ONS)

	2005-2006	2007-2008	2009
Numero totale di donne invitate	3.882.465	4.618.502	2.464.701
Numero di donne aderenti all'invito *	2.225.032	2.579.655	1.370.272
Adesione all'invito	57%	56%	56%
Classi di età			
50-54	54%	53%	52%
55-59	60%	59%	59%
60-64	60%	60%	60%
65-69	56%	56%	58%
Numero di donne esaminate (nel periodo considerato) * *	2.229.568	2.554.759	
Numero di donne richiamate per approfondimenti	139.617	144.049	
Percentuale di donne richiamate per approfondimenti	6,3%	5,6%	
Numero di biopsie benigne	2.138	1.964	
Numero di carcinomi diagnosticati allo screening	**10.529**	**11.707**	
Numero di carcinomi duttali in situ diagnosticati allo screening	**1.215**	**1.421**	
Numero di carcinomi invasivi ≤ 10 mm diagnosticati allo screening	**2.892**	**3.258**	

** numero di donne che hanno accettato di fare una mammografia in seguito ad invito effettuato nel periodo considerato;*

** * numero di donne che hanno effettuato una mammografia nel periodo considerato, indipendentemente da quando è stato mandato l'invito.*

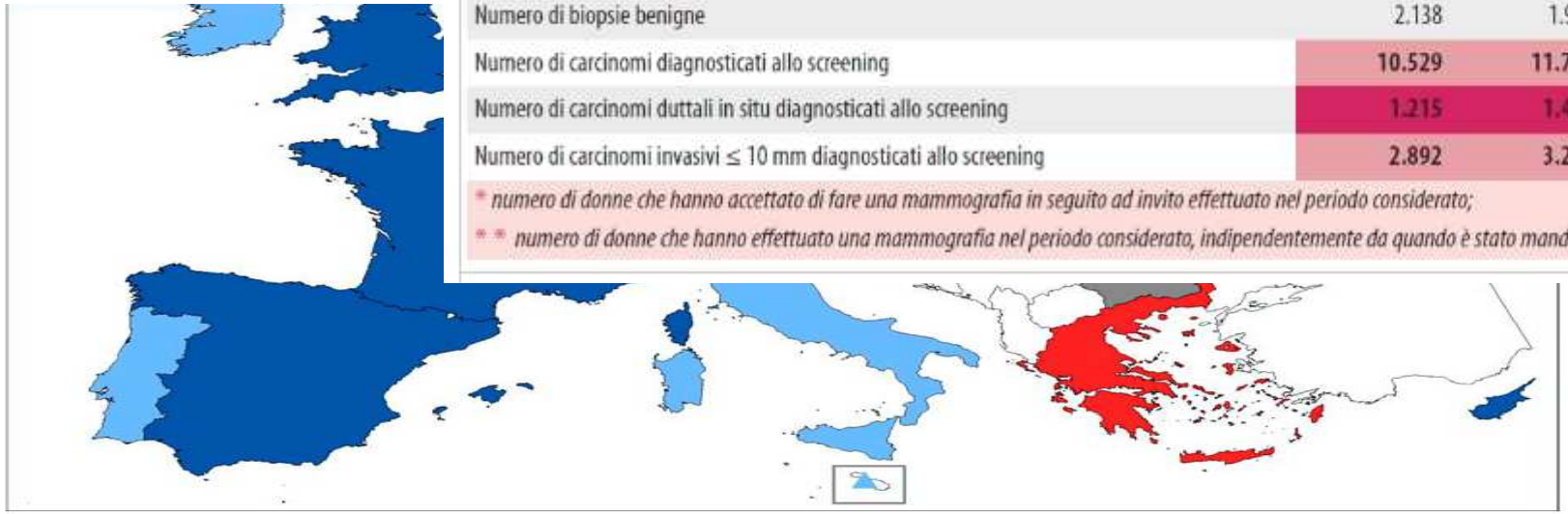

Figure 3 a. Breast screening programmes in the European Union in 2007, by programme type (population-based; non-population-based; no programme or unknown) and country implementation status (population-based: nationwide or regional, rollout complete or ongoing, , piloting and/or planning; non-population-based: nationwide or regional). For definitions see the text (section 2.3).

Source: European Commission (DG SANCO, 2007); IARC (ECN and EUNICE projects, 2007)

Br. J. Cancer (1989), 59, 954–958

Breast cancer screening programmes: the development of a monitoring and evaluation system

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Summary It is important that the introduction of breast screening is closely monitored. The anticipated effect on breast cancer mortality will take 10 years or more fully to emerge, and will only occur if a succession of more short-term end points are met. Data from the Swedish two-county randomised trial provide targets that should be achieved, following a logical progression of compliance with the initial invitation, prevalence and stage distribution at the prevalence screen, the rate of interval cancers after the initial screen, the pick-up rate and stage distribution at later screening tests, the rate of interval cancers after later tests, the absolute rate of advanced cancer and finally the breast cancer mortality rate. For evaluation purposes, historical data on stage at diagnosis is desirable; it is suggested that tumour size is probably the most relevant variable available in most cases.

- Int J Cancer. 1990 Aug 15;46(2):198-202.
- Early indicators **of efficacy of breast cancer screening programmes. Results of the Florence District Programme.**
- Paci E, Ciatto S, Buiatti E, Cecchini S, Palli D, Rosselli del Turco M.
- **Source**
- Centro per lo Studio e La Prevenzione Oncologica, Epidemiology Unit, Florence, Italy.
- **Abstract**
- A mammographic breast cancer screening programme has been ongoing in the Florence District (Italy) since 1970 and a favourable impact of screening on breast cancer mortality of women aged 50-70 has been shown by means of a case-control study. Two hundred and eleven screen- and 116 interval-detected cancers in the period 1975-1986 have been identified, and detection rates calculated, for first and repeated screening test (2nd to 7th). Overall, 22,980 subjects were screened and 44,988 repeated tests performed. The observed number of interval cancers has been compared with the expected incident cancers and their ratio (O/E) studied at different time intervals since last test. The O/E ratio at the third year since the last test was 0.98 for the age-group 40-49 0.50 (95% CI: 0.23-0.95) and 0.39 (95% CI: 0.26-0.94) for the 50-59 and 60-69 groups, respectively. The prevalence/incidence ratio (P/I) was then calculated as an early indicator of efficacy. For the 40-49 age-group the P/I ratio at first test was 1.09, suggesting poor anticipation of diagnosis. In contrast, for women 50-59 and 60-69 results suggest quite a good diagnosis anticipation (P/I: 3.14; 4.82), confirming the result of the previous case-control study on mortality reduction. The proportion of advanced carcinomas (stage II or worse) and 5-year survival have been analysed and discussed. The study confirms the opportunity of using early indicators of screening efficacy for monitoring of screening services.

Roadblocks

Cancer Registries and Service Screening

Critical issue: Linkage of cancer registry cases with screening database

- Early indicators (screened ad/or population based) evaluation
  1. Interval cancer cases
  2. Cancer characteristics, in particular pTNM , grade and biological markers
  3. Surgical and chemo-radio treatment
- Outcome evaluation
  1. Diagnostic modalities of all cases (Invited (Screen detected, interval, others) and not invited)
  2. Mortality within incident cancer cases, by diagnostic modality

Original article

Annals of Oncology 14: 1312–1325, 2003
DOI: 10.1093/annonc/mdg353

Measuring progress against cancer in Europe: has the 15% decline targeted for 2000 come about?

Conclusions: Cancer deaths in the EU were expected to rise from 850 194 in 1985 to 1 033 083 in 2000. It is estimated that there will be 940 510 cancer deaths that year, due to the decline in risk observed since 1985. The Europe Against Cancer programme appears to have been associated with the avoidance of 92 573 cancer deaths in the year 2000. With few exceptions, most countries are experiencing declining trends in cancer death rates, which seem set to continue, at least in the near future. Renewed tobacco control efforts are clearly needed for women, and there is a strong case for the introduction of organized breast and cervix screening programmes in all member states. Continuing to emphasize prevention within cancer control will help to promote the continuing decline in death rates in the future.

Background: Against a background of increasing cancer rates in the mid-1980s, *Europe Against Cancer* launched an ambitious programme aiming to reduce cancer mortality by 15% by the year 2000. A programme of activities and research, focussing on three major themes [prevention (particularly tobacco control), screening, and education and training], was developed together with the *European Code Against Cancer*.

EUROSCREEN WG

- Data presented are confidential and they are **in press** in a Supplement of the Journal of Medical Screening expected in August 2012
- Please no photo

Methodological methods used to estimate the effect of cancer screening on mortality from that cancer:

- **Analysis of mortality temporal trends**
- **Survival analysis**
- **Cohort studies**
- **Dynamic population (demographic) studies**

- **Incidence-based mortality**
- **Case control study**

Incidence-based mortality studies based on demographic population

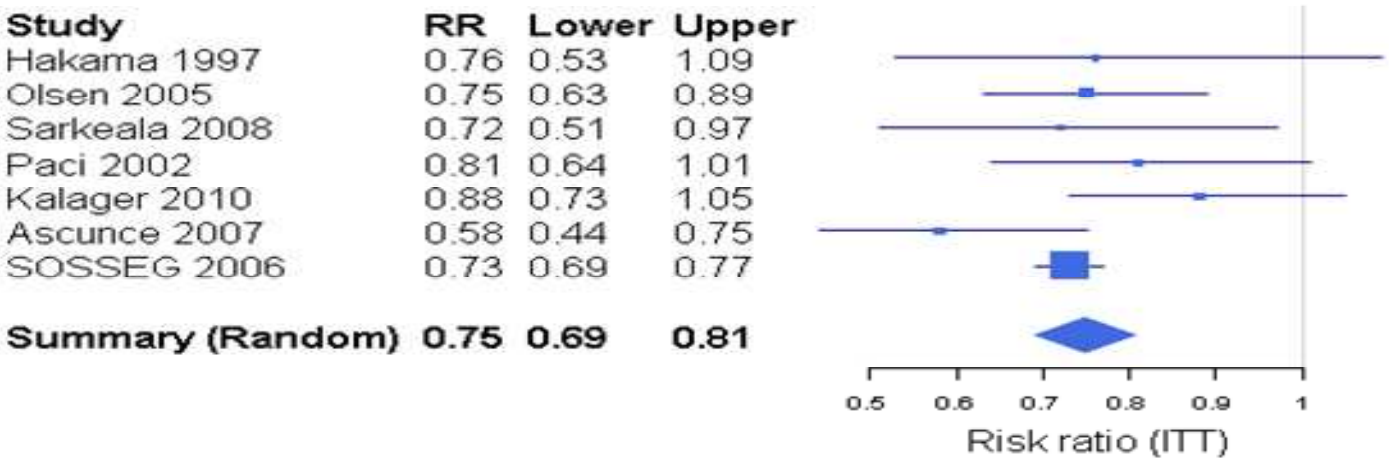
The comparison between invited and uninvited women may be correctly addressed using the incidence based mortality (IBM) method, where women with breast cancer diagnosed prior to their first invitation are excluded from the analysis.

The IBM rate is different from the usual mortality rate because the population at diagnosis rather than at deaths forms the denominator: person years at risk were counted from date of first invitation until date of death, emigration or end of follow-up.

CONFIDENTIAL

Review of the impact of population-based screening with mammography on breast cancer mortality in Europe (M.Broeders etal, EUROSCREEN WG)-

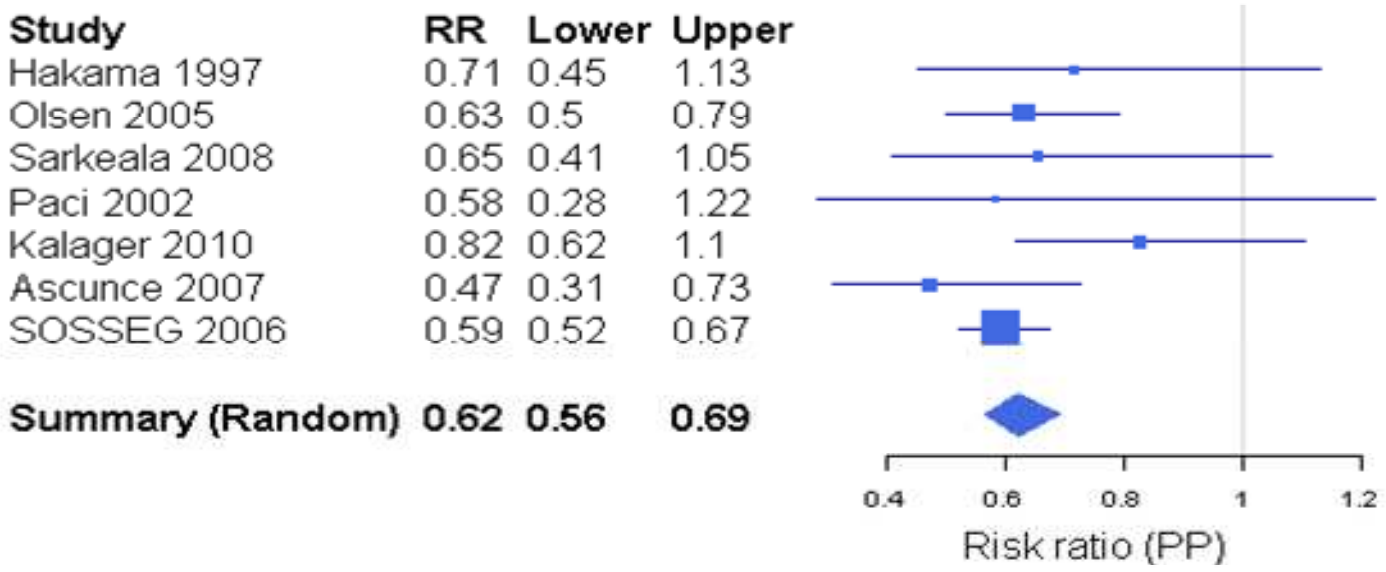
Figure 1a: Synthesis of IBM studies excluding overlapping data – estimates for breast cancer mortality reduction in women invited vs. not invited.



CONFIDENTIAL

Review of the impact of population-based screening with mammography on breast cancer mortality in Europe (M.Broeders etal, EUROSCREEN WG)-

Figure 1b: Synthesis of IBM studies excluding overlapping data – estimates for breast cancer mortality reduction in women screened vs. not screened.



IBM studies -EU

- Few studies
- Most with limited statistical power
- Methodology ,study design and follow up duration vary
- Most used aggregated ,not individual data, without classification by modality of diagnosis

- Need for methodological research

Case-control studies

The case-control study is a traditional tool for the evaluation of the effect of screening on BC mortality. The case-control study design has been used in several studies because of its efficiency.

The rationale of these studies is the comparison of the screening histories in two groups of women, namely:

1) those who have died from breast cancer (cases)

2) women sampled from the source population from which cases were drawn (controls).

It can designed as nested in cohort or in a dynamic population

The collection of screening histories of a limited number of subjects allows a more accurate and valid evaluation than it could obtain for the entire population.

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original article

Annals of Oncology
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Breast cancer screening case–control study design: impact on breast cancer mortality

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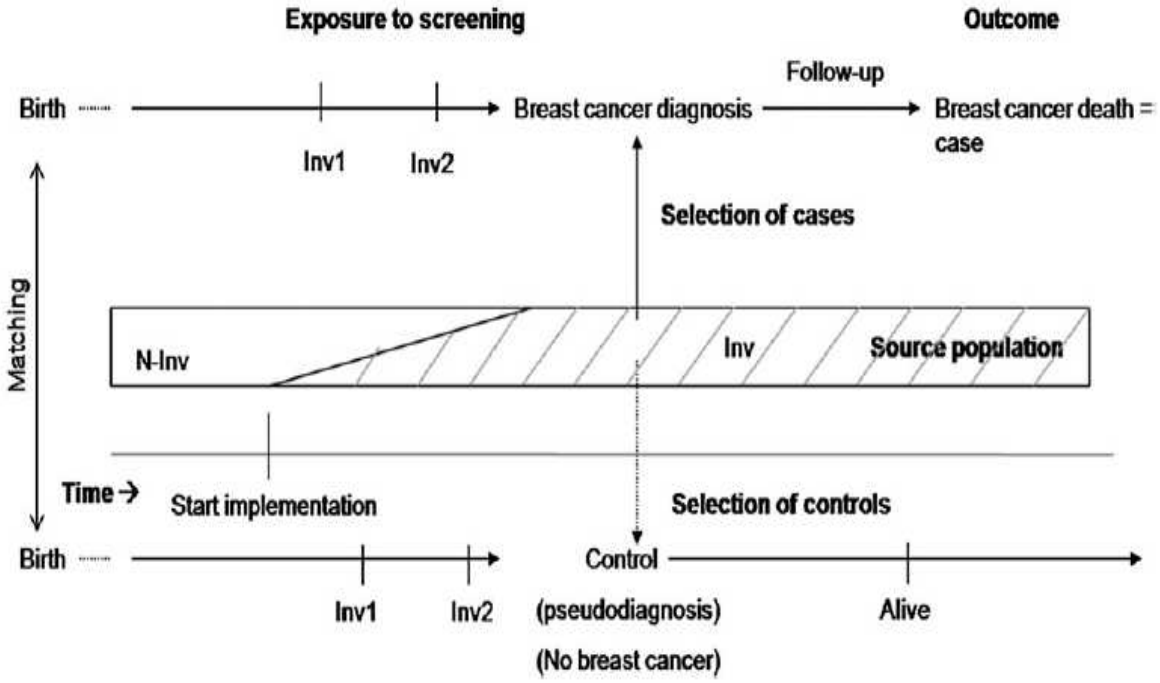

Figure 1. Design of the case–control studies for screening. Inv1, invitation 1 of case and control; Inv2, invitation 2 of case and control; N-Inv, not-invited women; Inv, invited women.

Effect estimate for ever/never screened, screened at the index invitation, number of screens and time since last screen

	Country	Ever–never, OR (95% CI)	Index invitation	Number of screens		Time since last screen (years)	
t al. [1]	UK (East Anglian region)	0.35 (0.24–0.51)		None	2.51 (1.56–4.03)	Never	1.71 (1.03
				1	1	<1	1
				2	0.70 (0.43–1.11)	1–2	0.43 (0.24
				3+	1.03 (0.59–1.77)	2–4	0.48 (0.28
						4+	0.55 (0.29
al. [19]	Wales	0.62 (0.47–0.82)		None	1	Never	1
				1	0.65 (0.48–0.88)	<0.5	1.57 (0.92
				2	0.64 (0.43–0.96)	0.5–1	0.43 (0.22
				3+	0.38 (0.19–0.72)	1–2	0.42 (0.25
						2–4	0.59 (0.39
						4+	0.58 (0.36
l. [2]	Iceland	0.59 (0.41–0.84)		None	1	Never	1
				1	0.60 (0.40–0.90)	<2	0.63 (0.43
				2	0.63 (0.38–1.03)	2–3	0.68 (0.36
				3	0.42 (0.22–0.80)	3–5	0.42 (0.18
				4	0.67 (0.31–1.42)	5+	0.38 (0.18
				5+	0.61 (0.21–1.74)		
l. [20]	Netherlands (IKL region)		0.30 (0.14–0.63)				
al. [3]	Italy	0.46 (0.38–0.56)					
al. [4]	Australia	All ages: 0.59 (0.47–0.74)		Frequent[b]	0.47 (0.34–0.65)	≤3	0.57 (0.44
		Age 50–69: 0.54 (0.41–0.72)		Other	0.64 (0.50–0.82)	>3	0.70 (0.47

of screens and time since last screen corrected for SES and health service access.

cy of recent screening: ≥3 screening rounds at ≤30-month intervals immediately preceding diagnosis.

dence interval; IKL, Comprehensive Cancer Centre Limburg; OR, odds ratio; SES, socioeconomic status.

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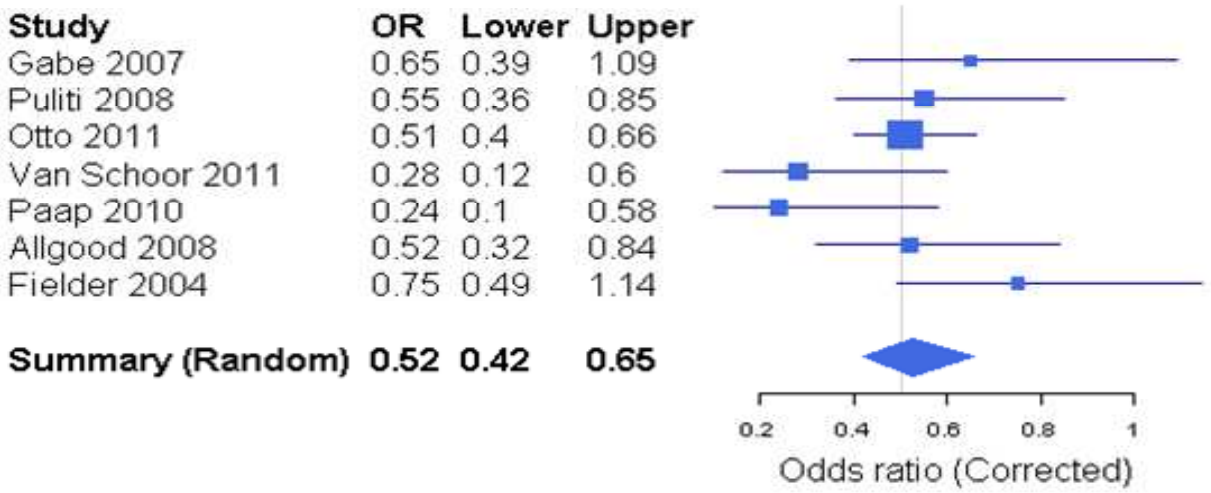
Review of the impact of population-based screening with mammography on breast cancer mortality in Europe (M.Broeders etal, EUROSCREEN WG)-

Figure 2b: Synthesis of case-control studies excluding overlapping data – odds ratios for breast cancer mortality reduction, corrected for self-selection, in women screened vs. not screened.



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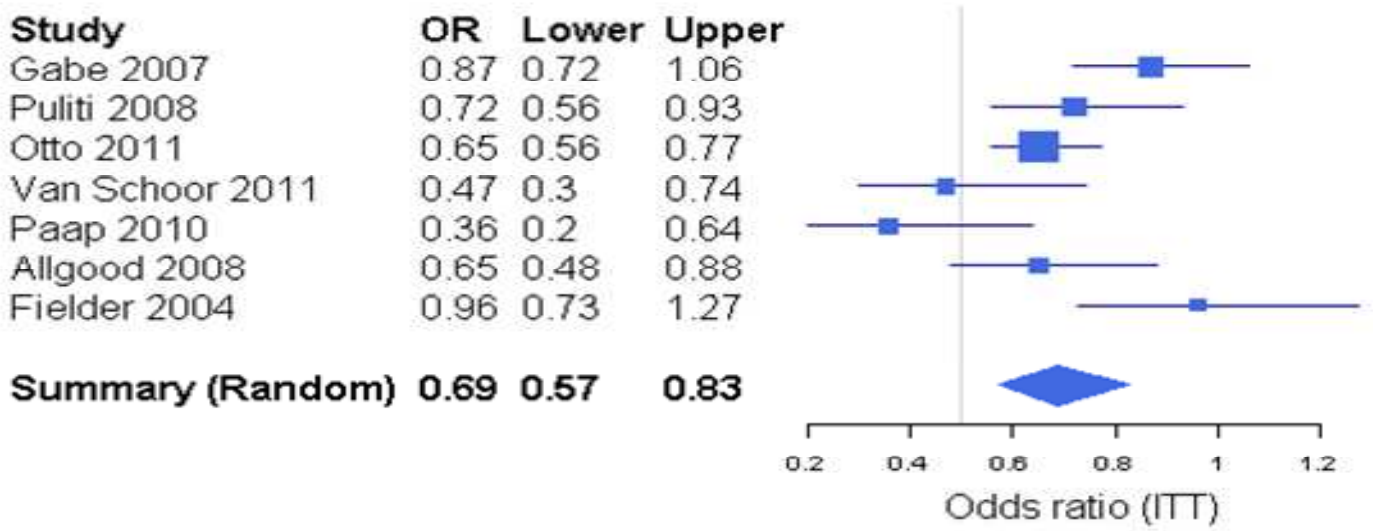
Review of the impact of population-based screening with mammography on breast cancer mortality in Europe (M.Broeders etal, EUROSCREEN WG)-

Figure 2c: Synthesis of case-control studies excluding overlapping data – crude odds ratios for breast cancer mortality reduction translated to intention to treat estimates for women invited vs. not invited.



British Journal of Cancer (2008) 99, 423–427

www.bjcancer.com

Effectiveness of service screening: a case–control study to assess breast cancer mortality reduction

D Puliti[1], G Miccinesi[1], N Collina[2], V De Lisi[3], M Federico[4], S Ferretti[5], AC Finarelli[6], F Foca[7], L Mangone[8], C Naldoni[6], M Petrella[9], A Ponti[10], N Segnan[10], A Sigona[11], M Zarcone[12], M Zorzi[13], M Zappa[1] and E Paci*[,1], the IMPACT Working Group

Table 2 The odds ratios for risk of breast cancer death by screening history

	No of cases/ controls	Odds ratio (95% CI)
Analysis by allocation		
Not-yet-invited	1093/4228	1
Invited[a]	657/2772	0.75 (0.62–0.92)
Analysis by screening status		
Unscreened[b]	1453/5282	1
Screened	297/1718	0.50 (0.42–0.60)
Analysis by screening status among invited women only		
Never respondent	360/761	1
Screened	297/1307	0.46 (0.38–0.56)
Screened (self-selection corrected)		0.55 (0.36–0.85)

[a]Screened+never-respondent. [b]Never-respondent+not-yet-invited.

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Cancer Epidemiology, Biomarkers & Prevention

Research Article

Mammography Screening and Risk of Breast Cancer Death: A Population-Based Case–Control Study

Suzie J. Otto[1], Jacques Fracheboud[1], André L.M. Verbeek[2], Rob Boer[1], Jacqueline C.I.Y. Reijerink-Verheij[3], Johannes D.M. Otten[2], Mireille J.M. Broeders[2,4], Harry J. de Koning[1], for the National Evaluation Team for Breast Cancer Screening

Abstract

Background: Because the efficacy of mammography screening had been shown in randomized controlled trials, the focus has turned on its effectiveness within the daily practice. Using individual data of women invited to screening, we conducted a case–control study to assess the effectiveness of the Dutch population–based program of mammography screening.

Methods: Cases were women who died from breast cancer between 1995 and 2003 and were closely matched to five controls on year of birth, year of first invitation, and number of invitations before case's diagnosis. ORs and 95% confidence intervals (CI) for the association between attending either of three screening examinations prior to diagnosis and the risk of breast cancer death were calculated using conditional logistic regression and corrected for self-selection bias.

Results: We included 755 cases and 3,739 matched controls. Among the cases, 29.8% was screen-detected, 34.3% interval-detected, and 35.9% never-screened. About 29.5% of the never-screened cases had stage IV tumor compared with 5.3% of the screen-detected and 15.1% of the interval-detected cases. The OR (95% CIs), all ages (49–75 years), was 0.51 (0.40–0.66) and for the age groups 50–69, 50–75, and 70–75 years were 0.61 (0.47–0.79), 0.52 (CI 0.41–0.67), and 0.16 (0.09–0.29), respectively.

Conclusion: The study provides evidence for a beneficial effect of early detection by mammography screening in reducing the risk of breast cancer death among women invited to and who attended the screening.

Impact: This is the first case–control study that accurately accounts for equal screening opportunity for both cases and matched controls by number of invitations before case's diagnosis. *Cancer Epidemiol Biomarkers Prev; 1–8. ©2011 AACR.*

La monografia del progetto IMPATTO:

Indice

Pubmed publications:

- Zorzi M, Puliti D, Vettorazzi M et al. Mastectomy rates are decreasing in the era of service screening. A population.based study in Italy (1997-2001). *Br J Cancer* 2006; 95: 1265-8.

- Paci E, Miccinesi G, Puliti D et al, for the IMPACT Working Group. Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy. *Breast Cancer Research*. 2006; 8(6): R68.

- Coviello E, Miccinesi G, Puliti D, Paci E. e il gruppo dello studio IMPATTO. The hazard function. *Epidemiol Prev.* 2007; 31(6): 346-51.

- Paci E, Coviello E, Miccinesi G, Puliti D et al. Evaluation of service screening impact in Italy: the contribution of hazard analysis. *Eur J Cancer* 2008; 44:858-65.

- Bucchi L, Puliti D, Ravaioli A et al. Breast screening: lymph node status of interval cancers by interval year. *The Breast* 2008; 17: 477-83.

- Puliti D, G, Collina N et al. Effectiveness of service screening: a case-control study to assess breast cancer mortality reduction. *Br J Cancer* 2008; 99: 423-427.

- Goldoni CA, Bonora K, Ciatto S et al, for the IMPACT Working Group. Misclassification of breast cause of death in a service screening area. *Cancer Causes & Controls* 2008.

- Zorzi M, Guzzinati S, Puliti D, Paci E and the IMPACT Working Group. A simple method to estimate the episode and programme sensitivity of breast cancer screening programmes. *J Med screen* 2010; 17(3): 132-138.

THE IMPACT STUDY (ITALY)

INDIVIDUAL LINKAGE

Inclusion criteria:

All breast cancers, in situ and invasive, diagnosed in women aged 40-79 between 1988 and 2005 in 22 areas located in various areas of Italy.

Variables collected:

- ✓ Size and nodal status (TNM)
- ✓ Surgical treatment, grading, hystological type, presence of metastasis, dissection, sentinel lymph node..
- ✓ Biological characteristics (hormon receptor, MIB,..)
- ✓ Follow_up for status alive or deceased and cause of death (updated at 31 December 2006)

Method of detection

All cancer registry-based breast cancer cases were linked to the screening database and partioned by method of detection in five categories:

screen-detected

1) cases diagnosed at the first screening test (SD)

2) cases diagnosed at a repeated screening test (SD)

3) cases detected clinically following a negative screening test (include interval cancer)

4) cases in women never respondent

5) cases in women not yet invited

TIME PERIOD OF THE STUDY and NUMBER OF BREAST CANCER CASES:

Region	Centre	Period of study	Number of BC cases	Start year of screening
Piemonte	Torino	1988 - 2003	10350	1992-1998
Veneto	Verona	1997 - 2003	2396	1999-2001
	Rovigo	1996 - 2003	1060	1998-1999
	Treviso	1999 - 2003	1094	2003-2004
Lombardia	Varese	1990 - 2002	6761	2000-2003
	Sondrio	1997 - 2006	1127	2000-2001
Friuli Venezia-Giulia		2001 - 2005	4580	2006
Trentino Alto Adige	Trento	1996 - 2004	2418	2001
Emilia Romagna	Parma	1992 - 2005	4451	1997
	Reggio Emilia	1997 - 2005	3299	1994-2001
	Ferrara	1991 - 2004	4154	1997-1999
	Modena	1992 - 2006	7363	1995-2000
	Bologna	1997 - 2004	5699	1997-1999
	Romagna	1989 - 2004	9019	1996-2000
Toscana	Firenze	1990 - 2004	6592	1991-1998
Umbria	Perugia	1997 - 2003	1559	1997
Campania	Napoli	1998 - 2005	1607	1998 - 2005
Sicilia	Ragusa	1990 - 2004	1712	1993-2001
	Palermo	1999 - 2005	3760	2005
	Siracusa	1999 - 2002	728	2001
	Trapani	2002 - 2005	776	No
	Catania	2003 - 2005	1565	1999

The study included about
82.000 breast cancer
(both in situ and invasive)

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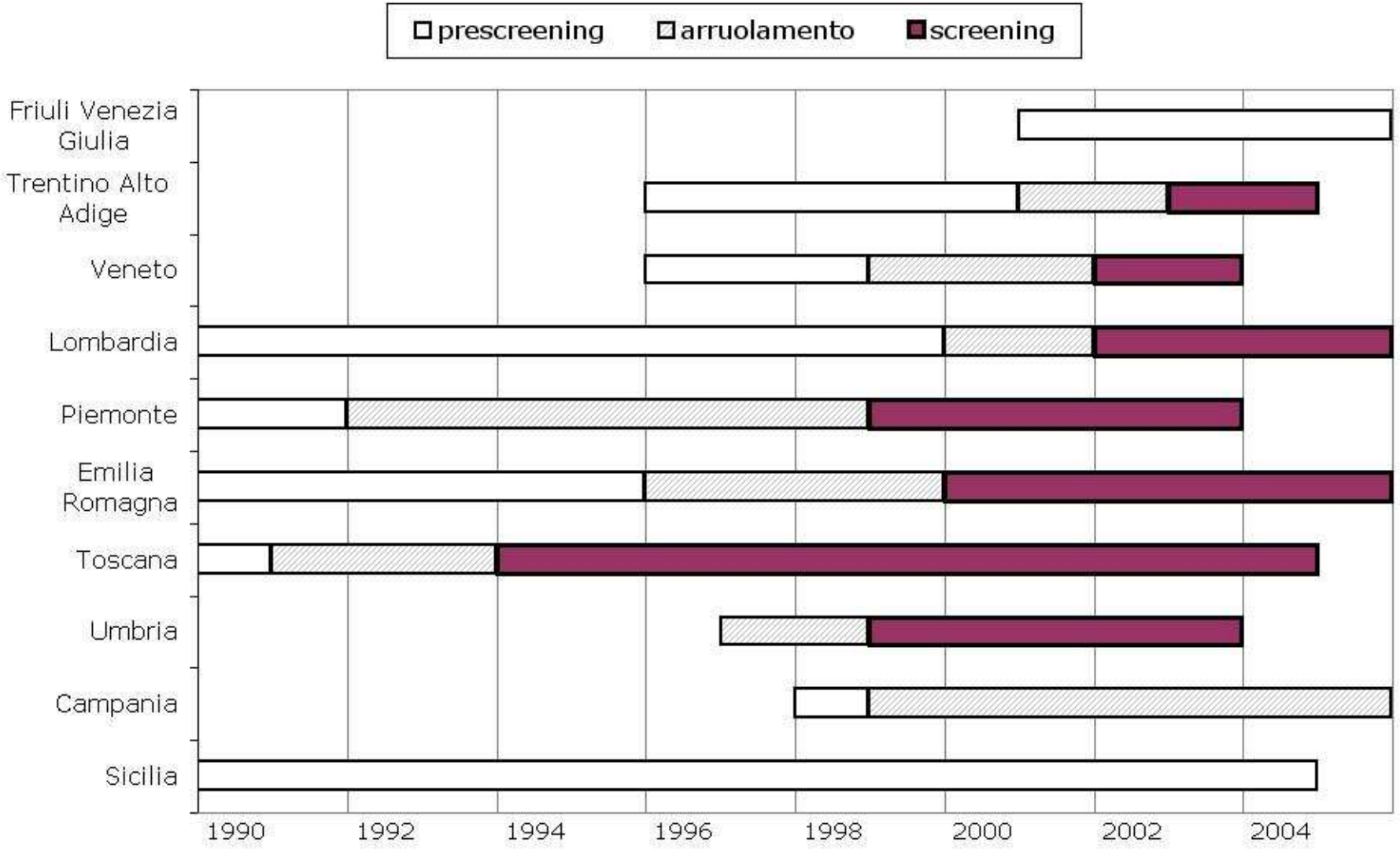
Study period by region: pre-screening, enrollment and screening phase



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Diagnostic Modality , by Region .
Age 50-69 anni. Period 1998-2006.

Regione	N°	SD (1°test)	SD (test ripet)	NSD screenate	NSD non rispondenti	NSD non invitate
Piemonte	2697	21.9	26.5	13.7	21.0	16.9
Lombardia	2281	16.6	4.3	2.9	7.5	68.7
Emilia Romagna	13733	21.8	28.3	15.4	19.3	15.3
Friuli Venezia Giulia	2503	0.0	0.0	0.0	0.0	100.0
Trentino Alto Adige	1061	23.8	7.0	4.9	9.1	55.3
Toscana	1903	11.2	37.4	25.8	18.7	7.0
Campania	842	7.7	2.5	4.4	16.9	68.5
Sicilia	3738	3.1	1.2	1.3	5.8	88.7

The florentine study: a cohort approach (Puliti et al., Breast Cancer Research, 2011)

The aim of this study is to define a balance sheet of benefits (breast cancer mortality reduction) and harms (overdiagnosis) for mammography screening programmes.

We compared breast cancer incidence and mortality in two cohorts of women – defined as "attenders" or "non-attenders" on the basis of the individual attitudes towards screening - who were invited to the first round of the Florentine screening programme.

Definition of the cohort

The cohort included the 52,282 women aged 50-69 years invited to the first screening round of the Florentine screening programme (1991-93).

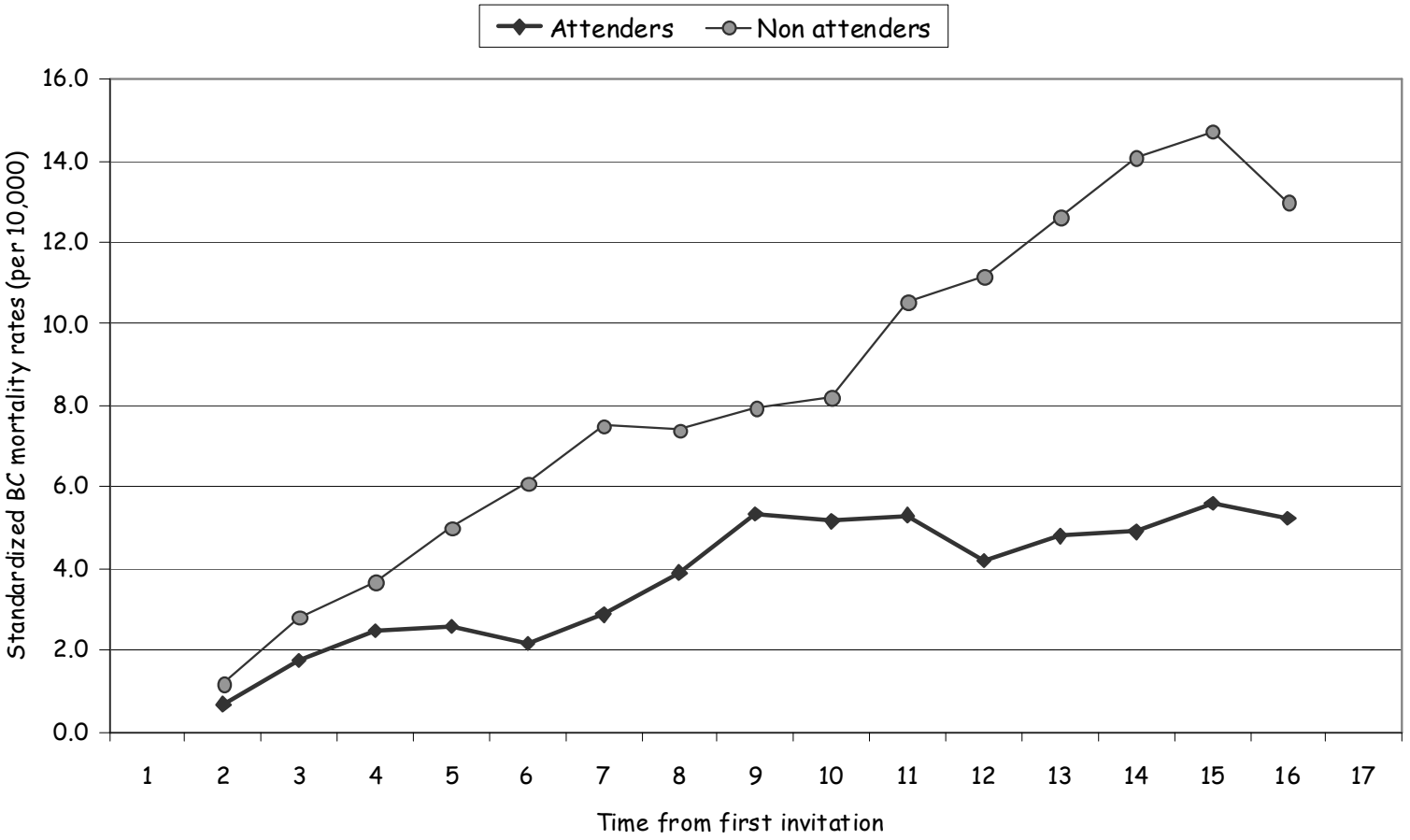
Definition of the exposure to screening

Screening exposure was defined on the basis of attendance at the first two rounds and the women were classified in:

1) *attenders*, if they responded at least to one invitation in the first two rounds,

2) *not attenders*, if they not responded to any of the first two invitations.

Standardized mortality rates from breast cancers (per 10.000) by time from first invitation. Women aged 50-69 years at entry.



The effects of screening exposure on breast cancer incidence and mortality were evaluated by fitting Poisson regression models adjusted for age at entry, marital status and deprivation index.

Breast cancer mortality

Age at entry	Exposure	BC deaths	Person years	BC mortality rate (per 10,000)	Adjusted rate ratio (*)
50-59	Non-attenders	77	113 409	6.8	1
	Attenders	90	270 399	3.3	0.55 (0.41 - 0.75)
60-69	Non-attenders	141	151 615	9.3	1
	Attenders	94	233 543	4.0	0.49 (0.38 - 0.64)

Breast cancer incidence

Age at entry	Exposure	BC cases (**)	Person years	BC incidence rate (per 1,000)	Adjusted rate ratio (*)
50-59	Non-attenders	321	105 635	3.0	1
	Attenders	838	249 896	3.4	1.15 (1.01 - 1.31)
60-69	Non-attenders	461	142 547	3.2	1
	Attenders	745	216 309	3.4	1.10 (0.98 - 1.23)

Major problems

- Analysis per protocol
- How much compliance rates influence the mortality rates of participants
- how much are mortality rates different from the rates before screening?
- How to consider the underlying trend?

- In Italy we are evaluating a study cohort of about 500.000 invited

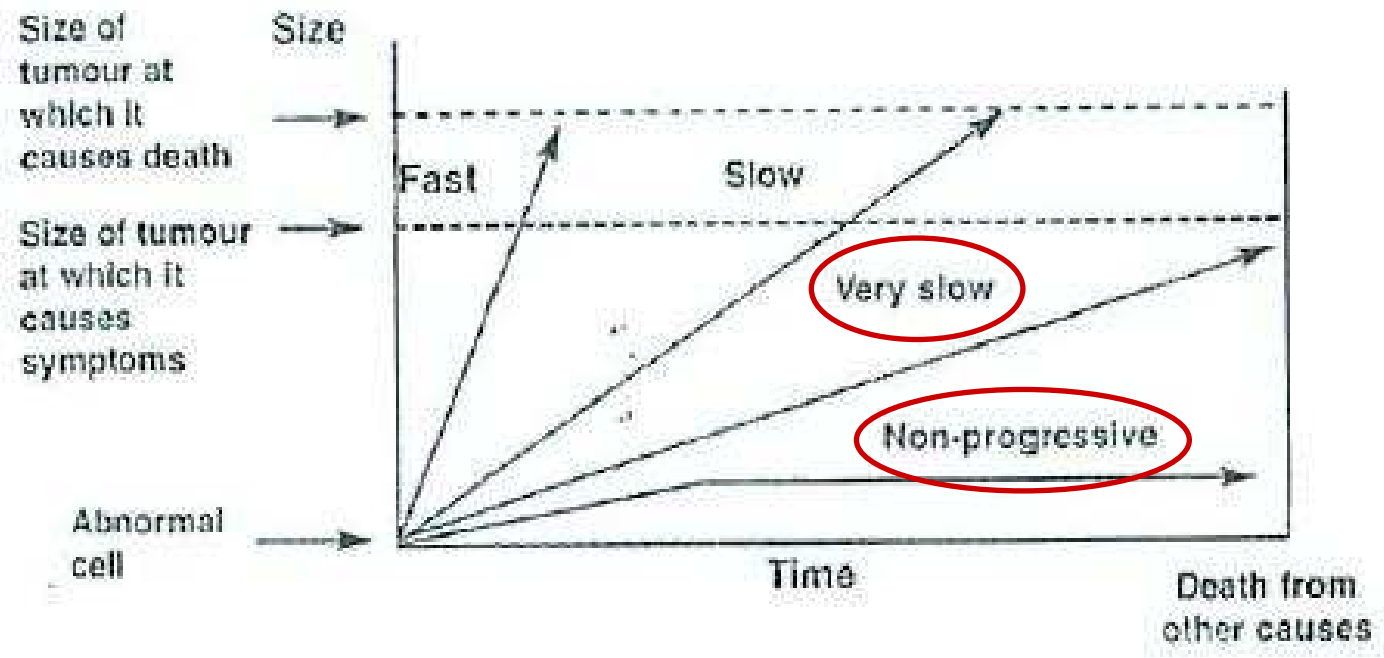
Balance of Benefits and Harms

- Service screening outcomes should be evaluated in terms of benefits but also potentially adverse effecs
- Most important adverse effects are
  - Overdiagnosis
  - Mastectomy and BCS rates
  - False Positive rates
  - Radiation risk

Overdiagnosis

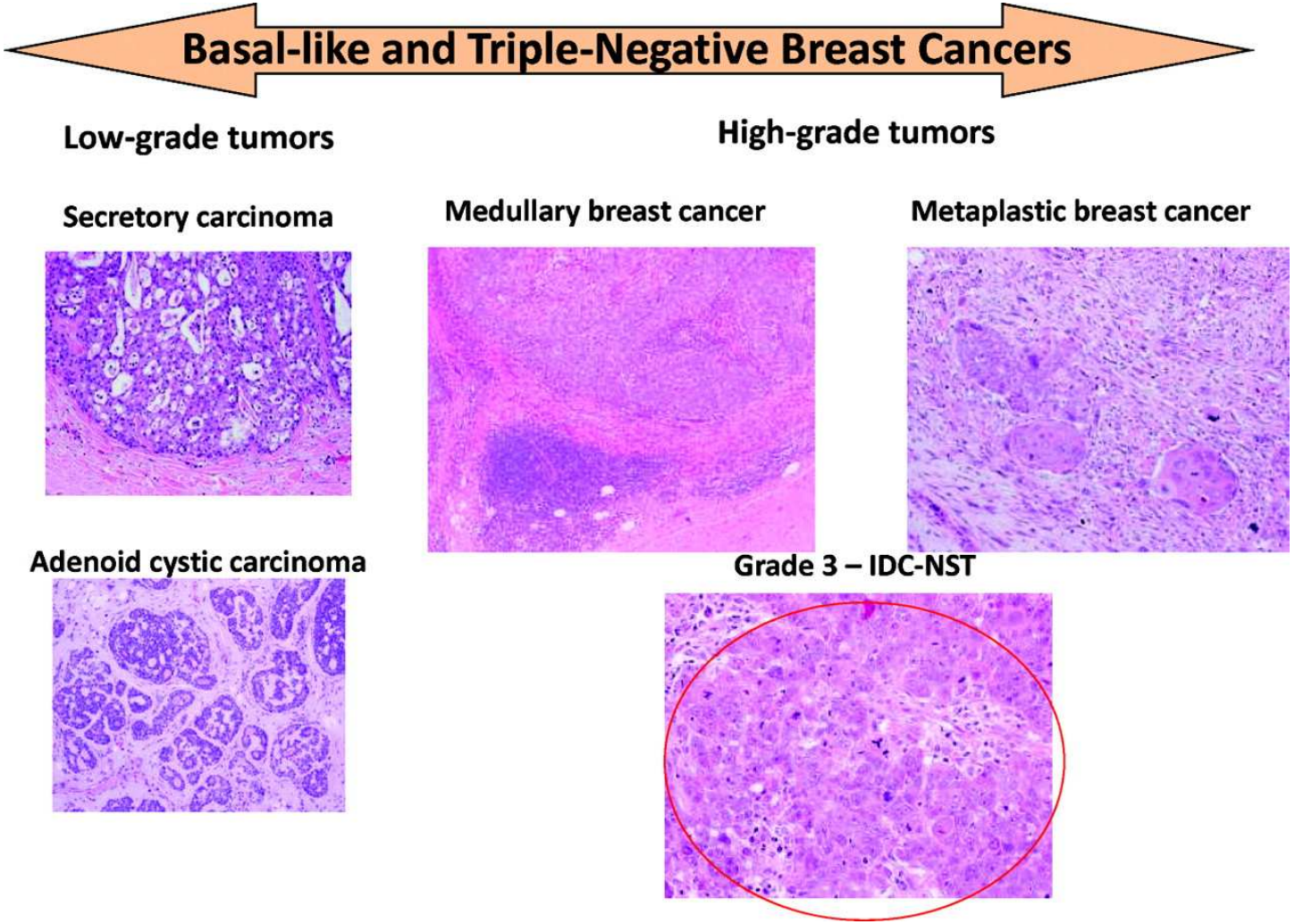
- **Overdiagnosis is usually defined as the proportion of confirmed cancer cases (invasive and in situ) diagnosed during a screening episode that would not have come to clinical attention if screening had not taken place.**

Growth rates of cancers (IARC, 2002)



The diagnosis of these cancers (very slow and non-progressive), that Morrison (1975) have called "pseudodisease", is overdiagnosis. At that time observed in lung cancer screening trials and after in prostate cancer screening.

Triple-negative breast cancer: Range of histology.



Hudis C A , Gianni L The Oncologist 2011;16:1-11

Overdiagnosis and breast cancer

"Detection of in situ or invasive breast cancers at screening that would have never clinically surfaced in the absence of screening"

It's the combination of two causes:

1. the natural history of the disease (low or no potential to progress to symptomatic disease)

2. the presence of competing causes of death (potentially progressive cancer in a subject who is going to die of other causes in the near future)

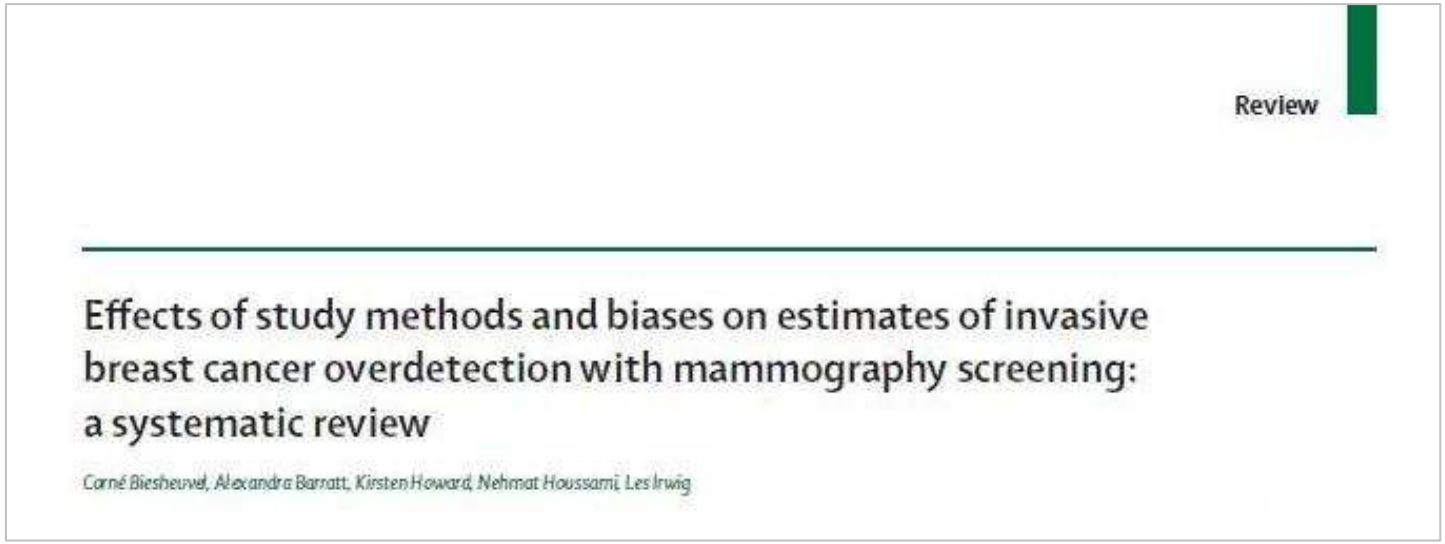
Paci and Duffy, Breast Cancer Research, 2005

The Clinician and Epidemiologist/Researcher perspective

The clinician knows there are less aggressive, slow growing breast cancer cases, usually with good prognosis but today it is difficult do not treat , just wait and see. To discriminate potential aggressiveness is the challenge of research

- The epidemiologist / the clinician as researcher look backward at the excess of the diagnosed breast cancer cases, but they can not evaluate who has been overdiagnosed or who has not received benefit from treatment

STUDY METHODS TO ESTIMATE OVERDETECTION:



"The theoretically most robust method to estimate overdetection 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 overdetection will be too high." (adjusted for lead-time method)

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

Estimate of the excess of incidence /overdiagnosis
after 15 years
since the screening cycle end: about 10%

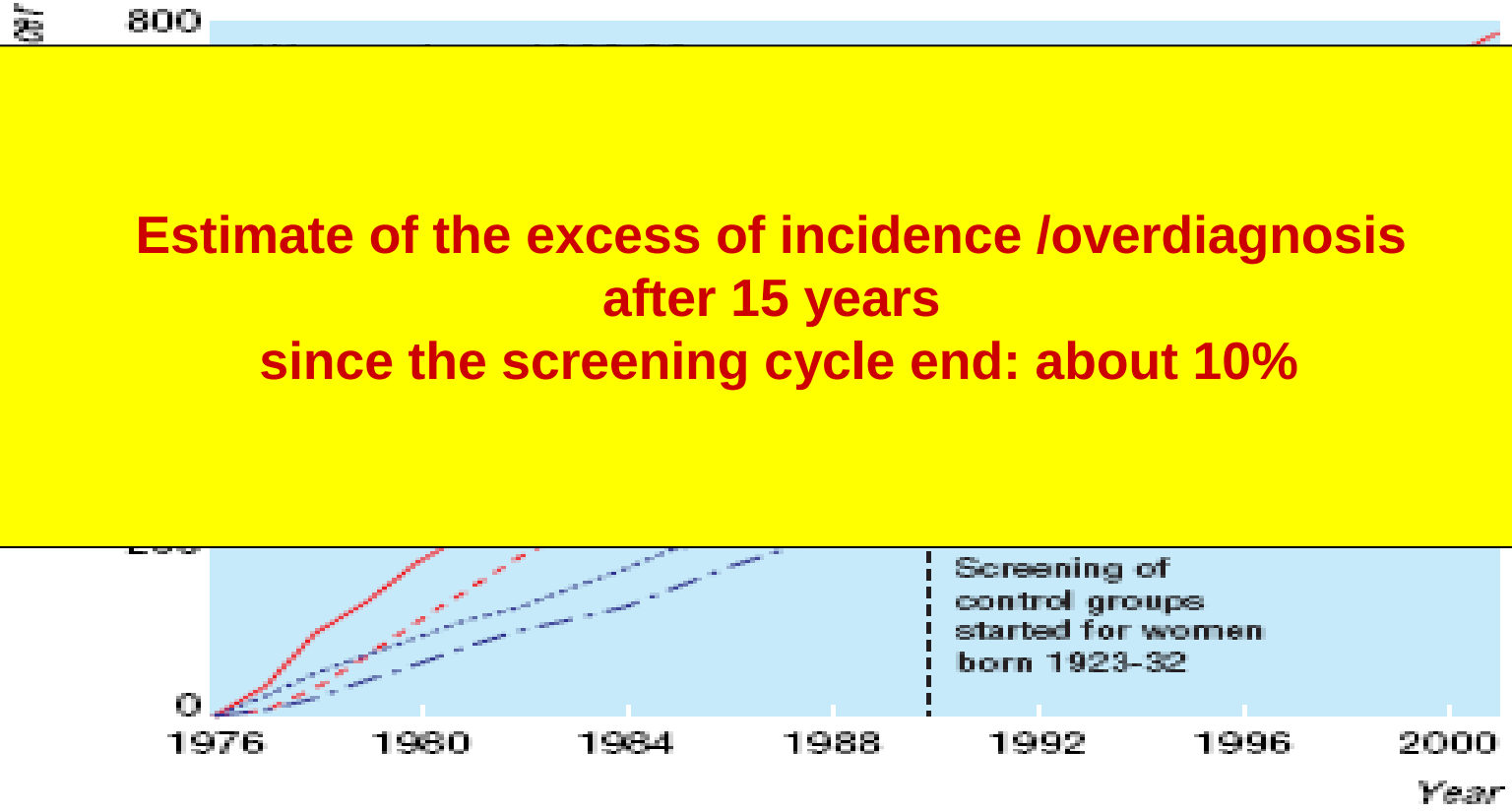


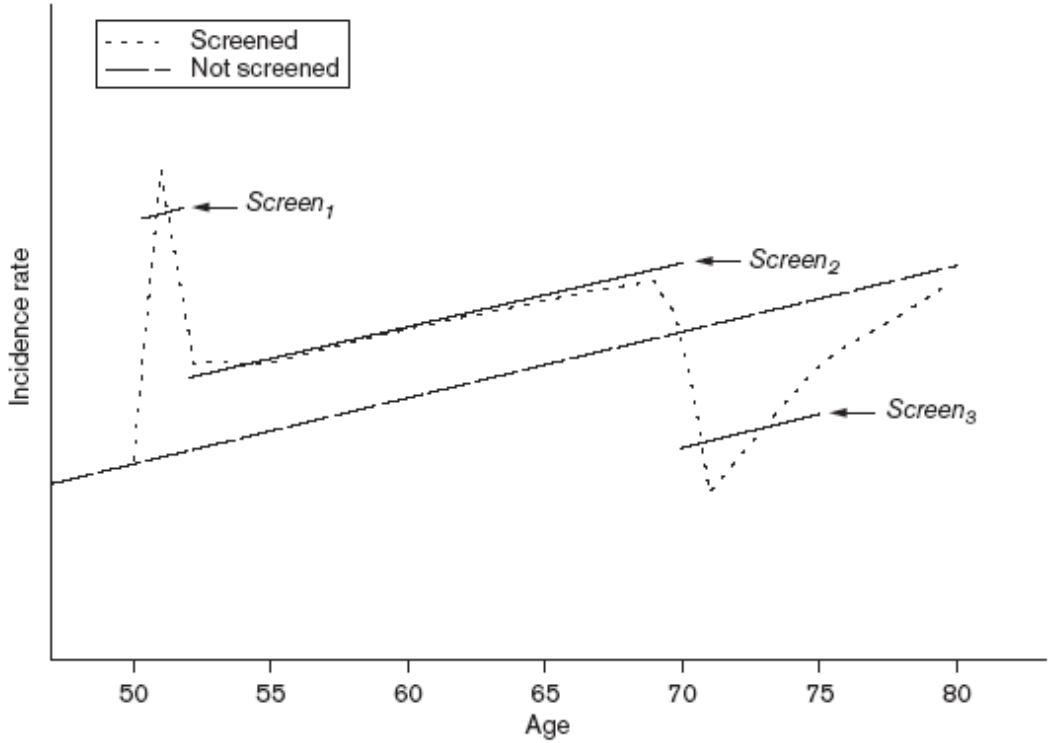
Fig 2 Cumulative number of all breast cancer cases (in situ and invasive) per year and group for total follow-up of women born during 1908-22 (unscreened control group) and 1923-32 (controls groups invited to screening from 1990 onwards)

The influence of mammographic screening on national trends in breast cancer incidence

B Møller[1], H Weedon-Fekjær[1], T Hakulinen[2], L Tryggvadóttir[3], H H Storm[4], M Talbäck[5] and T Haldorsen[1]

European Journal of Cancer Prevention 2005, 14:117–128

Fig. 1



Hypothetical impact of screening women every 2 years between 50 and 69 years of age. *Screen*$_1$, *screen*$_2$ and *screen*$_3$ are the effects of the initial screening round, subsequent screening rounds, and post screening, respectively.

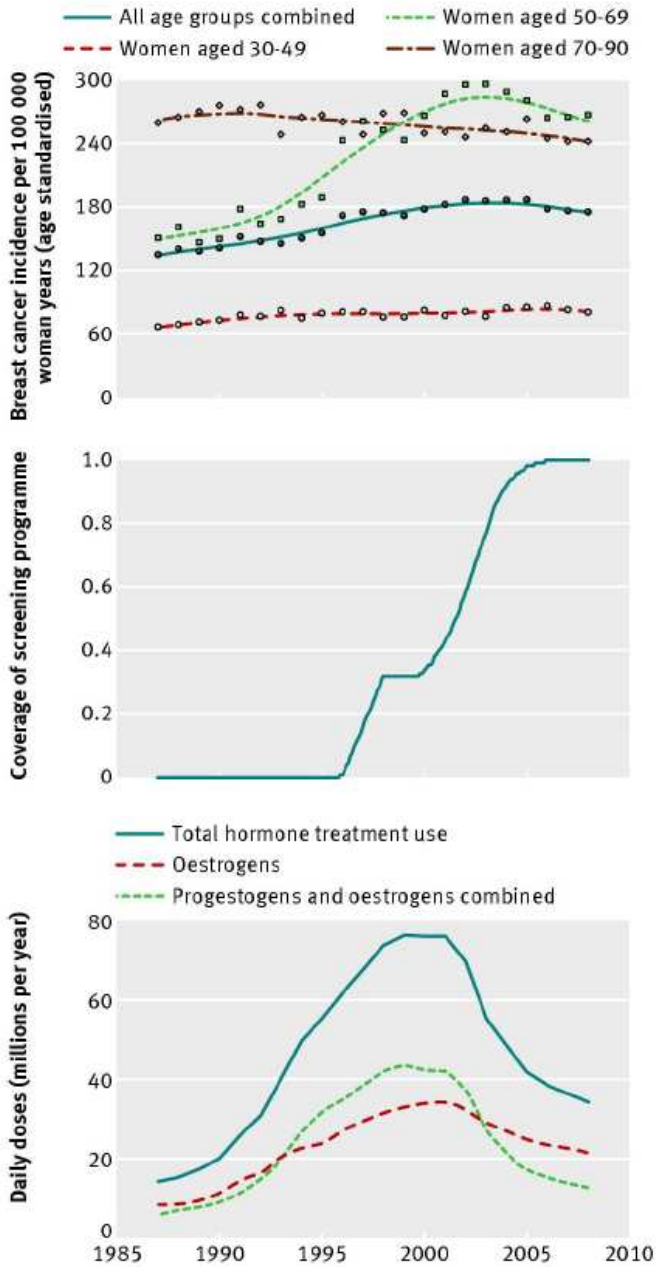
Methods – study design

- The cumulative incidence approach is still used in very few observational studies
- Most studies evaluated incidence in demographic populations, not following up individual women over time.
- Major problems in analysis are :
  - How consider the compensatory drop after the screening cycle end (or statistical adjustment for lead time)
  - The methodology of adjustment for underlying risk in the absence of screening (in the absence of a control group)

Understanding recent trends in incidence of invasive breast cancer in Norway: age-period-cohort analysis based on registry data on mammography screening and hormone treatment use

Harald Weedon-Fekjær *statistician*[1], Kjersti Bakken *associate professor*[2], Lars J Vatten *professor*[3], Steinar Tretli *research director, and professor*[1 3]

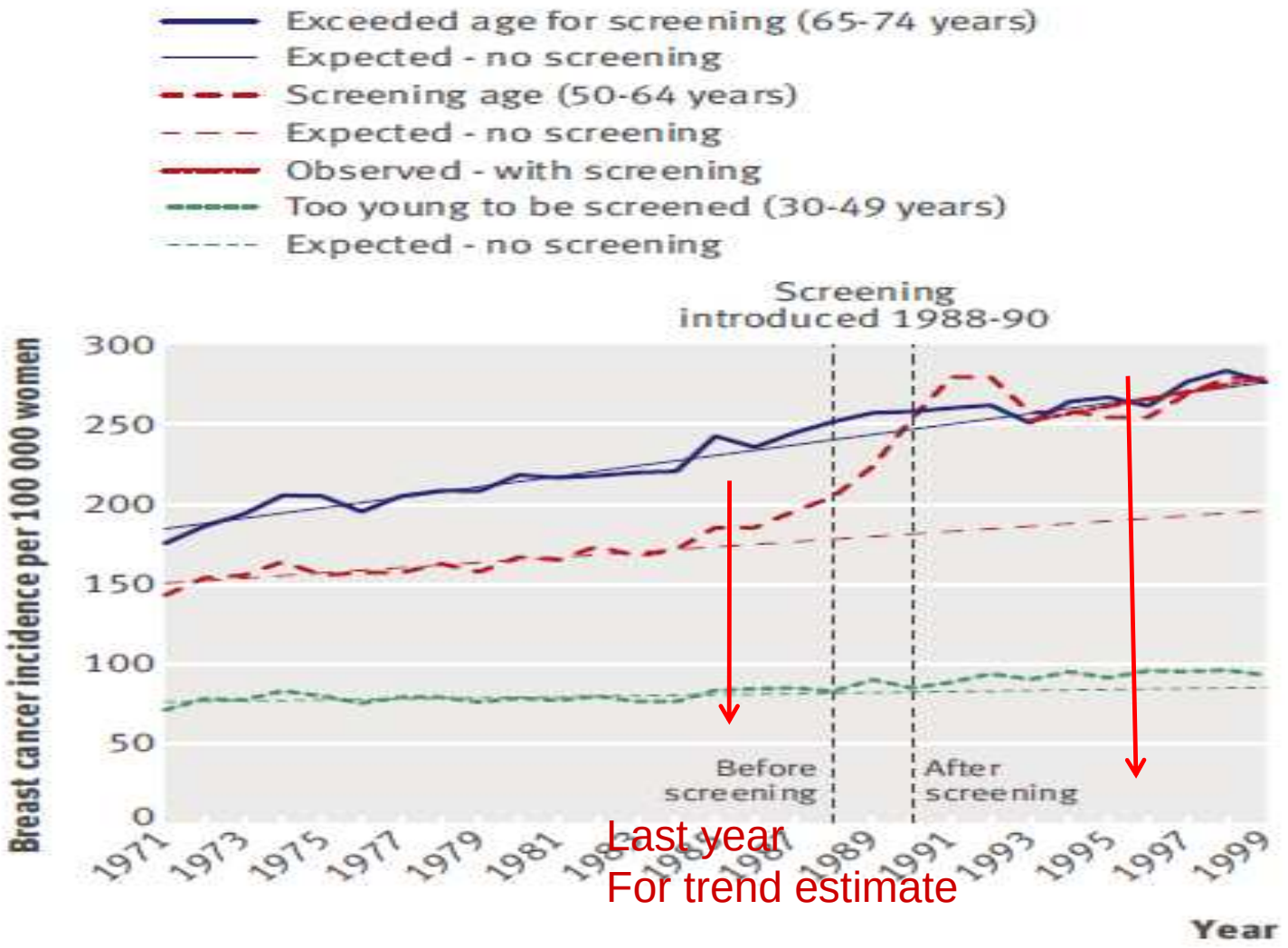
[1]Department of Etiological Research, Cancer Registry of Norway, Institute of Population-based Cancer Research, PO Box 5313 Majorstuen, 0304 Oslo, Norway; [2]Department of Community Medicine, University of Tromsø, Norway, and University of Bergen, Norway; [3]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway



Estimates of the trend in the absence of screening- demographic population approach

- Jorgensen, 2009
- Duffy, 2010
- Same data (UK)
- Different estimate of the trend
- Different age groups

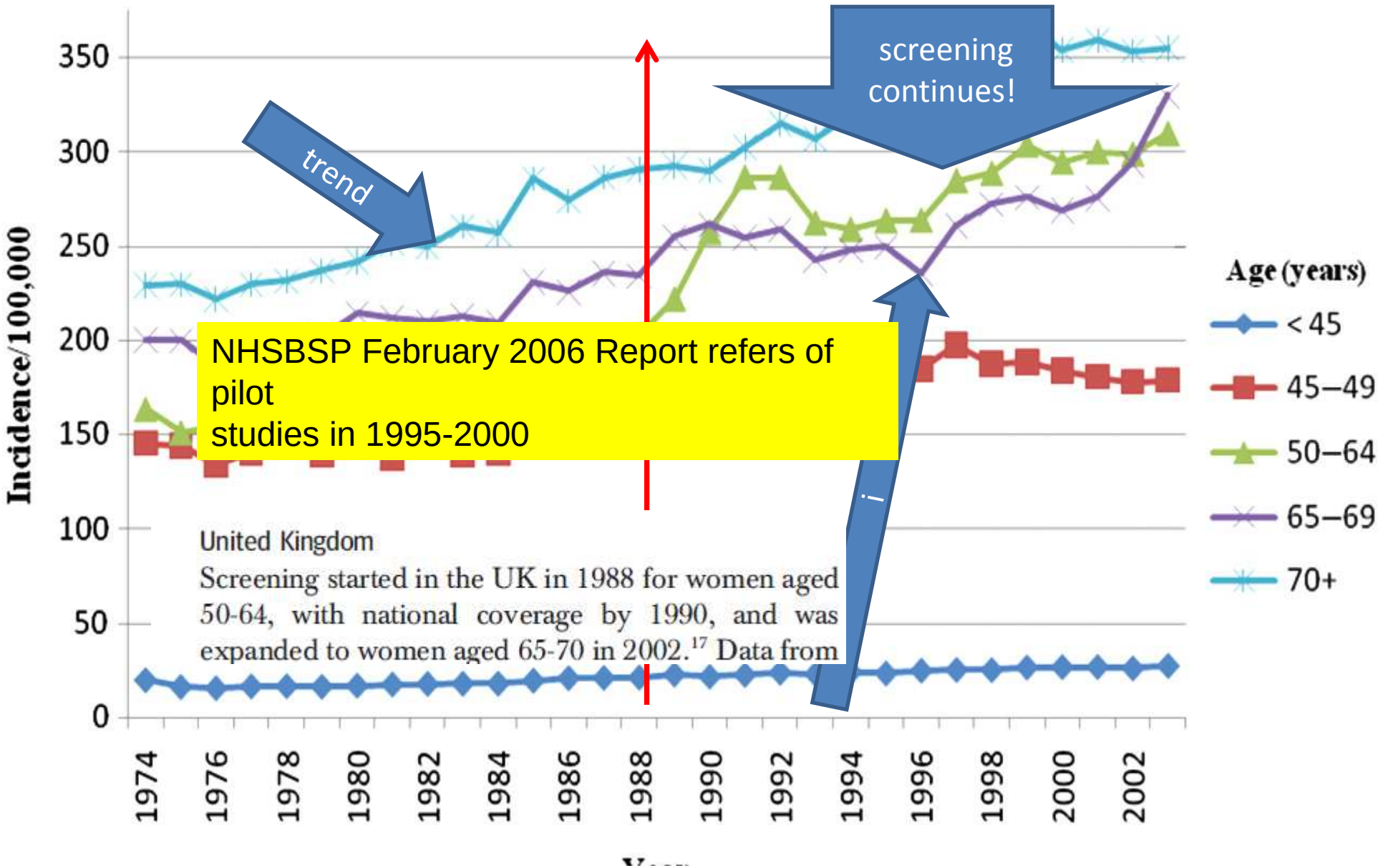
Jorgensen 2009



AGE 65-74

Fig 2| Incidence of invasive breast cancer per 100 000 women in UK

UK Incidence , by age group (Cancer UK Duffy,2010)



BMJ

RESEARCH

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

Karsten Juhl Jørgensen, researcher Peter C Gøtzsche, director

The Nordic Cochrane Centre, Rigshospitalet, Dept 3343, Blegdamsvej 9, DK-2100 Copenhagen, Denmark

Correspondence to: KJ Jørgensen kj@cochrane.dk

Cite this as: *BMJ* 2009;339:b2587 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 Syste
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Data sources
authors.

Review meth
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Results Incid
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Conclusions
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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

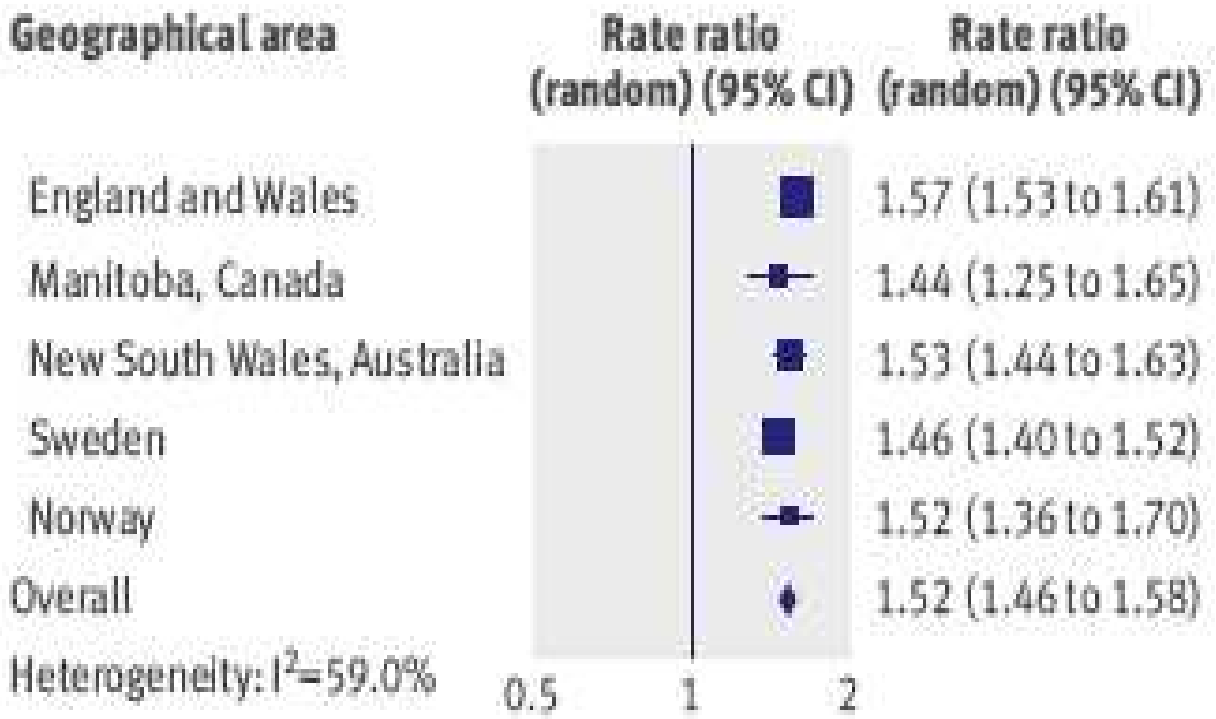

Fig 8 | Meta-analysis of overdiagnosis of breast cancer (including carcinoma in situ) in publicly available mammography screening programmes

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Conclusions The increase in incidence of breast cancer was closely related to the introduction of screening and little of this increase was compensated for by a drop in incidence of breast cancer in previously screened women. One in three breast cancers detected in a population offered organised screening is overdiagnosed.

been fully implemented, and including both screened and non-screened age groups, were available from the United Kingdom; Manitoba, Canada; New South Wales, Australia; Sweden; and parts of Norway. The implementation phase with its prevalence peak was excluded and adjustment made for changing background incidence and compensatory drop in incidence among older previously screened women. Overdiagnosis was estimated at 52% (95% confidence interval 46% to 58%). Data from three countries showed a drop in incidence as the women exceeded the age limit for screening, but the reduction was small and the estimate of overdiagnosis was compensated for in this review.

Conclusions The increase in incidence of breast cancer was closely related to the introduction of screening and little of this increase was compensated for by a drop in incidence of breast cancer in previously screened women. One in three breast cancers detected in a population offered organised screening is overdiagnosed.

lesions. Thirty seven per cent of women aged 40-54 who died from causes other than breast cancer had lesions of invasive or non-invasive cancer at autopsy, and half were visible on radiography.[3,4]

Overdiagnosis can be measured precisely in a randomised trial with lifelong follow-up if people are assigned to a screening or control group for as long as screening would be offered in practice, which in most countries is 20 years. Overdiagnosis would be the difference in number of cancers detected during the lifetime of the two groups, provided the control group or age groups not targeted are not screened. In the absence of overdiagnosis the initial increase in cancers in the screened age groups would be fully compensated for by a similar decrease in cancers among older age groups no longer offered screening, as these cancers would already have been detected.

The extent of overdiagnosis and overtreatment as a result of mammography screening was first quantified in reviews of randomised trials.[5,6] The total number of mastectomies and lumpectomies increased by 31%

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journal homepage: www.ejconline.com

An estimate of overdiagnosis 15 years after the start of mammographic screening in Florence

*Puliti Donella, Zappa Marco, Miccinesi Guido, Falini Patrizia, Crocetti Emanuele, Paci Eugenio**

Clinical and Descriptive Epidemiology Unit, ISPO – Cancer Prevention and Research Institute, via San Salvi 12, 50135 Florence, Italy

- The Florentine service screening programme, started in 1991, offers high-quality mammography every 2 years to all resident women aged 50 to 69.

- Breast cancer cases diagnosed in the target population are registered by the Tuscan Tumour Registry, which has been operating in the area since 1985.

Objective:

To evaluate the degree of overdiagnosis of breast cancer 15 years after the introduction of mammographic service screening in Florence in the year 1991.

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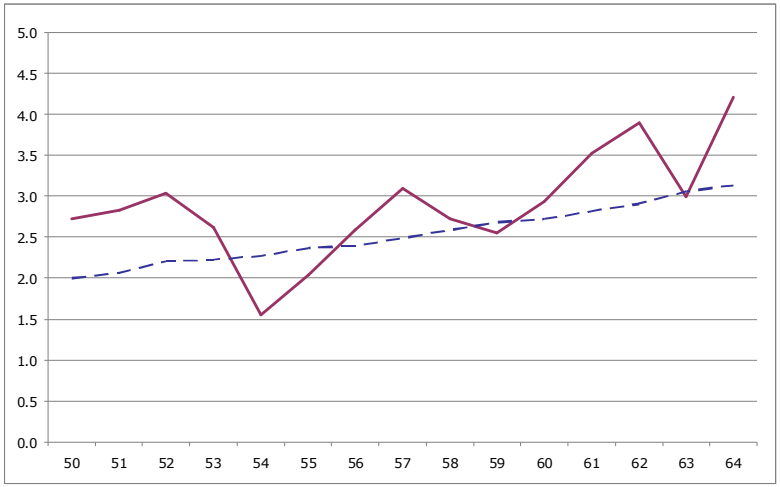
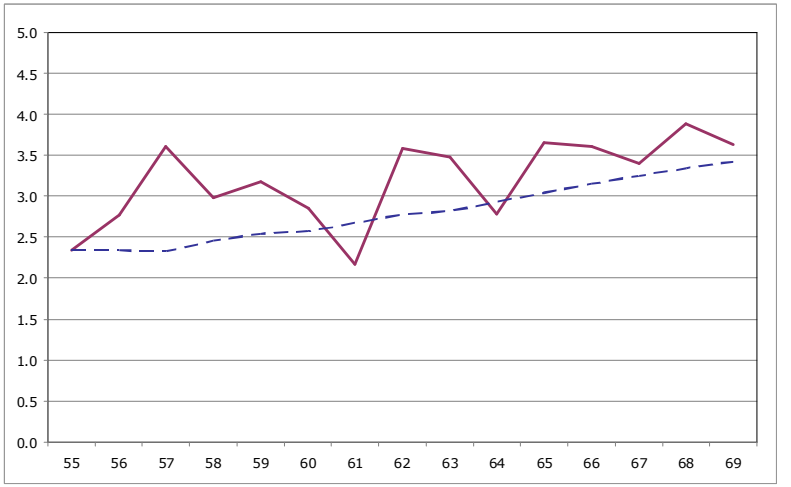
FIGURE 1. Invited (observed) and non-invited (expected) incidence breast cancer rates by age at the beginning of service screening:

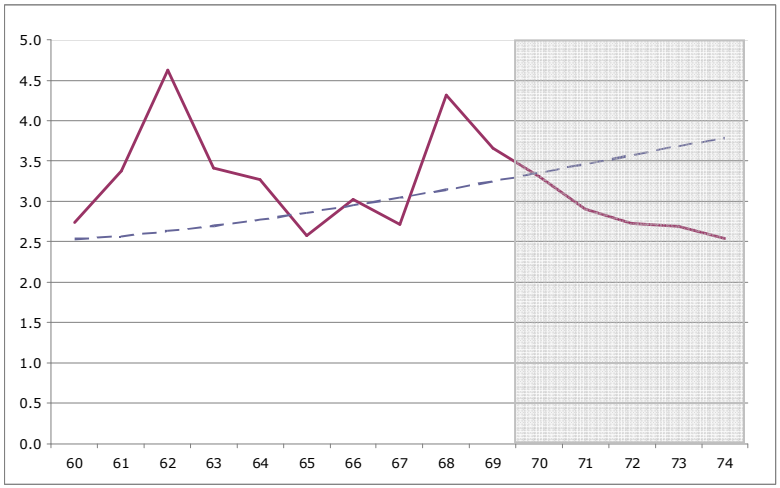
a) 50-54 years



b) 55-59 years



c) 60-64 years



d) 65-69 years

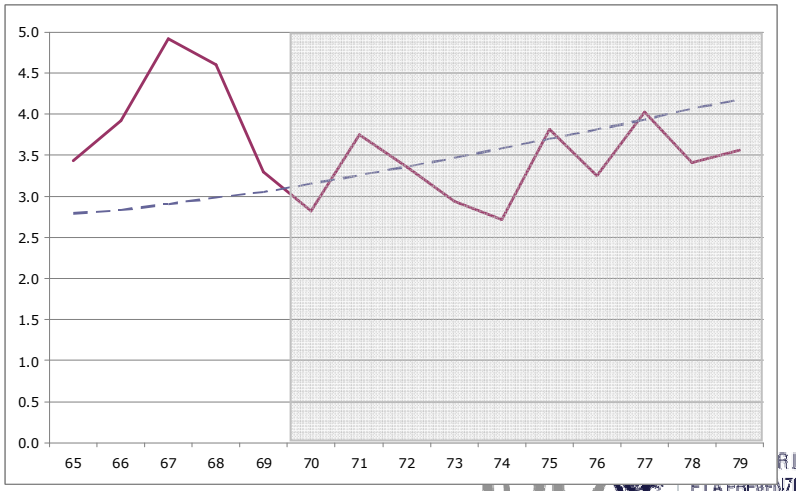
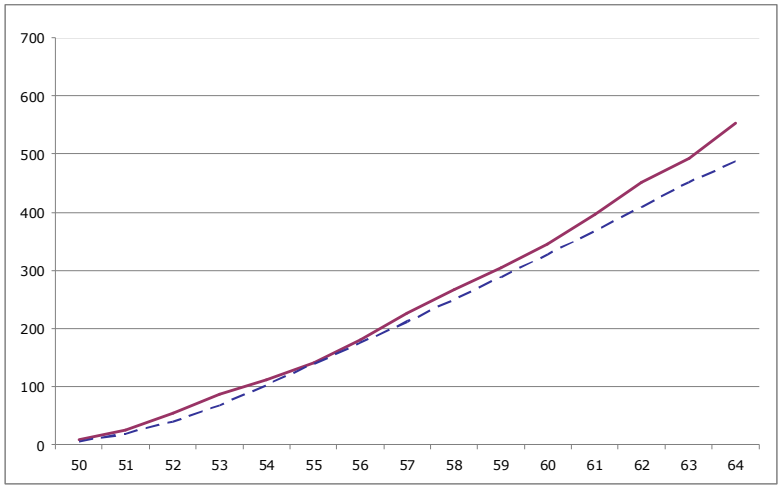
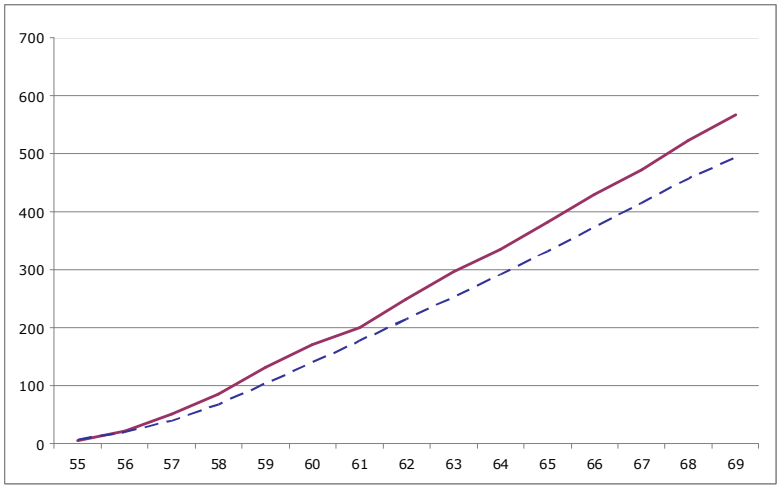


FIGURE 2. Invited (observed) and non-invited (expected) cumulative breast cancer cases by age at the beginning of service screening:

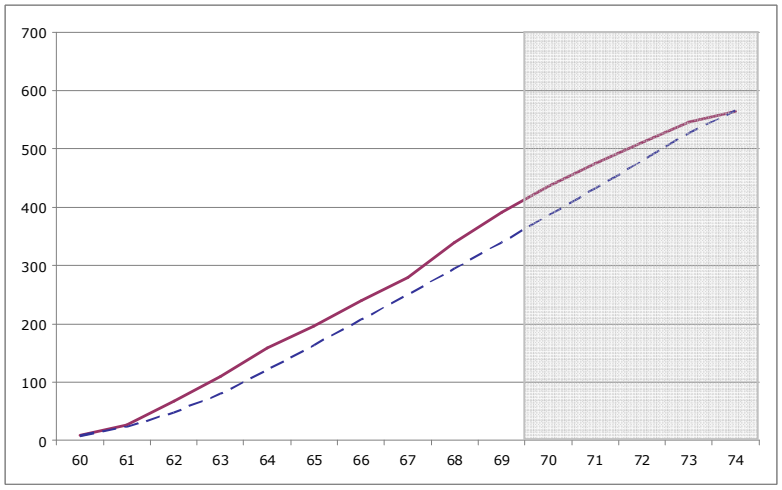
a) 50- 54 years



b) 55-59 years



c) 60-64 years



d) 65-69 years

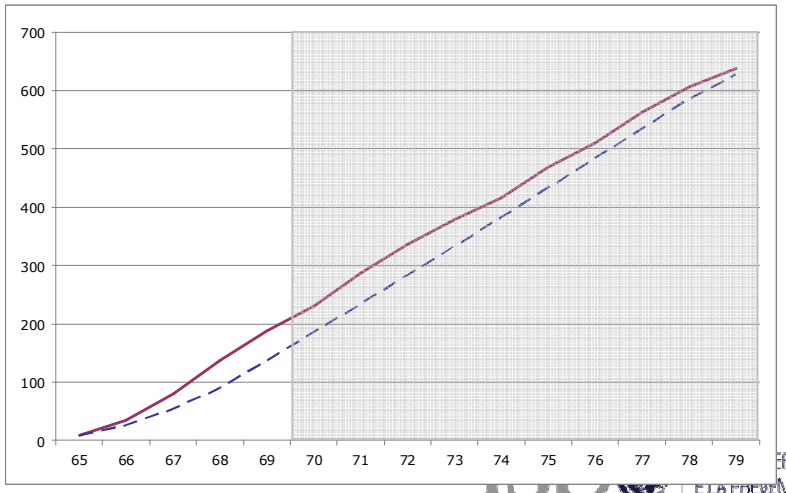


TABELLA 1.

Incidence excess and estimate of overdiagnosis by birth cohort.

Age at the start of service screening	Years of screening	Incidence excess (95%CI) in the last year of screening	Years after screening stopped	Estimate of overdiagnosis (95%CI)
50-54	**15**	1.15 (1.06 to 1.24)	**0**	n.e.
55-59	**15**	1.15 (1.06 to 1.25)	**0**	n.e.
60-64	**10**	1.15 (1.04 to 1.27)	**5**	0.99 (0.91 to 1.07)
65-69	**5**	1.36 (1.18 to 1.57)	**10**	1.01 (0.94 to 1.09)

1.00 (0.95 – 1.06)
for in situ and invasive cases

The effects of screening exposure on breast cancer incidence and mortality were evaluated by fitting Poisson regression models adjusted for age at entry, marital status and deprivation index. (Puliti et al., BCR,2011)

Breast cancer mortality

Age at entry	Exposure	BC deaths	Person years	BC mortality rate (per 10,000)	Adjusted rate ratio (*)
50-59	Non-attenders	77	113 409	6.8	1
	Attenders	90	270 399	3.3	0.55 (0.41 - 0.75)
60-69	Non-attenders	141	151 615	9.3	1
	Attenders	94	233 543	4.0	0.49 (0.38 - 0.64)

Breast cancer incidence

Age at entry	Exposure	BC cases (**)	Person years	BC incidence rate (per 1,000)	Adjusted rate ratio (*)
50-59	Non-attenders	321	105 635	3.0	1
	Attenders	838	249 896	3.4	1.15 (1.01 - 1.31)
60-69	Non-attenders	461	142 547	3.2	1
	Attenders	745	216 309	3.4	1.10 (0.98 - 1.23)

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 elegible for inclusion in this review.

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).

The studies were classified according with the method of adjustment for lead time and for temporal trend

EUROSCREEN WG: confidential, preliminary

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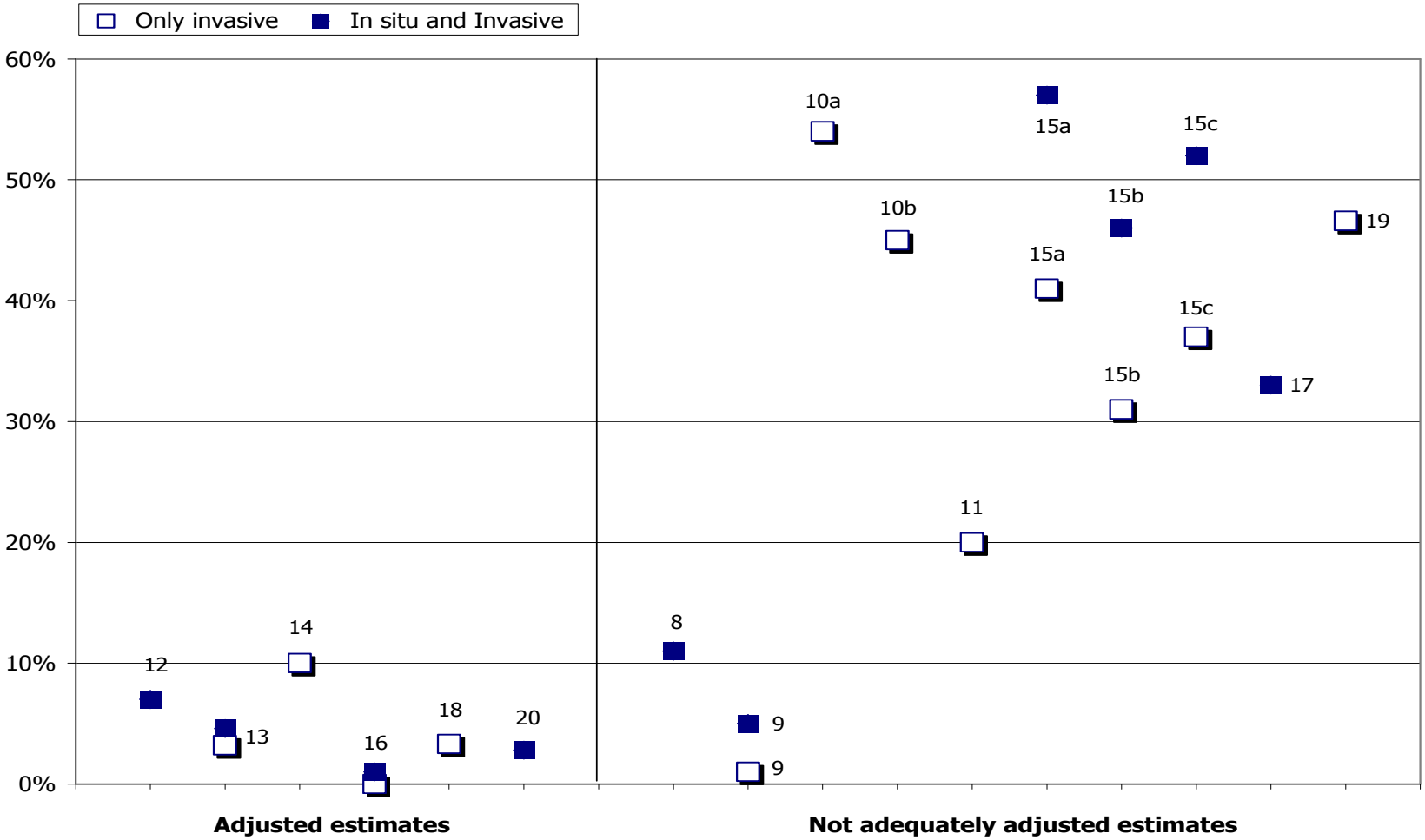
Paper	Adjustment for temporal trend	Adjustment for lead time	Estimate of overdiagnosis
Peeters, 1989	Not necessary	No	11.0%
Paci, 2004	No	Statistical adjustment	5.0%
Zahl, 2004	No	No	45%-54%
Jonsson, 2005	No	Statistical adjustment	0-54%
Olsen, 2006	Not necessary	Statistical adjustment	7.0%
Paci, 2006	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.



EUROSCREEN WG:confidential,preliminary

CONCLUSIONS

On the basis of this classification, the estimates of overdiagnosis adjusted for breast cancer risk and for lead time range from 1% to 10%:

2.8% in The Netherland,
4.6% and 1% in Italy,
7.0% in Denmark
10% and 3.3% in United Kingdom

Average of six corrected estimates = 6.5%

Not adequately adjusted estimates range from 0 to 54%.

EUROSCREEN WG:confidential,preliminary

Balance sheet: benefit and harms in service screening (Europe)

	Benefits	Harms
Estimates from the reviews	**Pooled estimates of mortality reduction among screened women range from 38% (IBM studies) to 48% (case-control studies)**	**Estimates of overdiagnosis adjusted for lead time and breast cancer risk range from 1% to 10%, with a corrected average estimate of 6.5%** **Estimates of cumulative risk of false positive results range from 8% to 21%, with a pooled estimate of 17% without invasive assessment and 3% with invasive assessment**
	Balance sheet	
For every 1000 women aged 50 years screened biennially until 69 years and followed until 79 years:	**7-9 women's lives are saved** **(out of 19 expected in the absence of screening)**	**4 women are overdiagnose** **(out of 67 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**

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

Rethinking Screening for Breast Cancer and Prostate Cancer

Laura Esserman, MD, MBA

Yiwey Shieh, AB

Ian Thompson, MD

After 20 years of screening for breast and prostate cancer, several observations can be made. First, the incidence of these cancers increased after the introduction of screening but has never returned to prescreening levels. Second, the increase in the relative fraction of early stage cancers has increased. Third, the incidence of regional cancers has not decreased at a commensurate rate. One possible explanation is that screening may be increasing the burden of low-risk cancers without significantly reducing the burden of more aggressively growing cancers and therefore not resulting in the anticipated reduction in cancer mortality. To reduce morbidity and mortality from prostate cancer and breast cancer, new approaches for screening, early detection, and prevention for both diseases should be considered.

JAMA. 2009;302(15):1685-1692

www.jama.com

BREAST CANCER AND PROSTATE cancer account for 26% of all cancers in the United States, with an estimated 386 560 patients diagnosed annually: 194 280 for breast cancer and 192 280 for prostate cancer[1] For both, there are remarkable differences between outcomes of localized vs advanced disease (breast cancer: 5-year relative survival rates of 98.1% vs 27.1%; prostate cancer: 100% vs

László Tabár, MD

Swedish Two-County Trial: Impact of Mammographic Screening on Breast Cancer Mortality during 3 Decades[1]

Radiology

Purpose: To estimate the long-term (29-year) effect of mammographic

There was a highly significant reduction in breast cancer mortality in women invited to screening according to both local end point committee data (relative risk [RR] = 0.69; 95% confidence interval: 0.56, 0.84; $P < .0001$) and consensus data (RR = 0.73; 95% confidence interval: 0.59, 0.89; $P = .002$). At 29 years of follow-up, the number of women needed to undergo screening for 7 years to prevent one breast cancer death
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cancer deaths would
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Invitation to mammo
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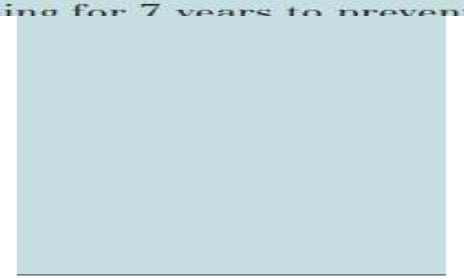
Radiology



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

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

Proponents of mammographic screening generally say that the benefit is large and established beyond

There have been substantial advances in treatment since most of the trials were performed, and these advances must

REVIEW

The Breast Screening Programme and misinforming the public

Peter C Gøtzsche • Karsten Juhl Jørgensen
The Nordic Cochrane Centre, Copenhagen, Denmark
Correspondence to: Peter C Gøtzsche. Email: pcg@cochrane.dk

DECLARATIONS

Summary

We hope the EUROSCREEN review will help to improve the debate

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Service screening and Surgical approach

- The increasing rates of BCS after screening start have been considered as a secondary benefit of screening. The increase of early stages facilitated the use of BCS
- The Proportion of BCS in screen detected cancer cases is very high, whereas some advanced breast cancers are screen detected, especially at prevalence screening

RESEARCH

THIS WEEK'S RESEARCH QUESTIONS

Surgery rates after breast cancer screening

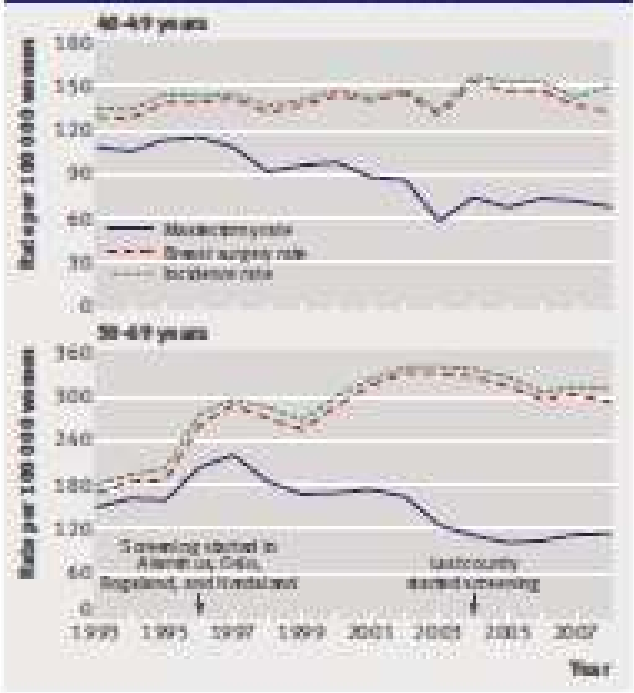
Among the coauthors of this paper by Pål Suhrke and colleagues (p 575), the names of Jørgensen and Gøtzsche should be familiar to *BMJ* readers from previous articles critical of mammographic breast screening programmes—in particular of the claimed benefits of screening. One of the supposed benefits is that discovering tumours at an earlier stage may reduce mastectomies by increasing the potential for breast conserving treatment.

However, this study of breast surgery rates during the stepwise introduction of screening in Norwegian counties finds an initial increase in mastectomies and an overall increase in surgery in the age group invited to screening (50-69 years). The authors suggest that over diagnosis is the cause—but as Richard Smith discussed in his *BMJ* blog this week (http://bit.ly/pduPKe), little is known about the rate of natural progression of ductal carcinoma in situ (DCIS), and when this is communicated to women in whom DCIS is discovered, many would rather have the lesion removed than live with uncertainty. A randomised controlled trial of watchful waiting and yearly mammography versus surgery for DCIS is under way, which may improve estimates of risk of natural progression of precancerous breast lesions.

Effect of mammography screening on surgical treatment for breast cancer in Norway: comparative analysis of cancer registry data

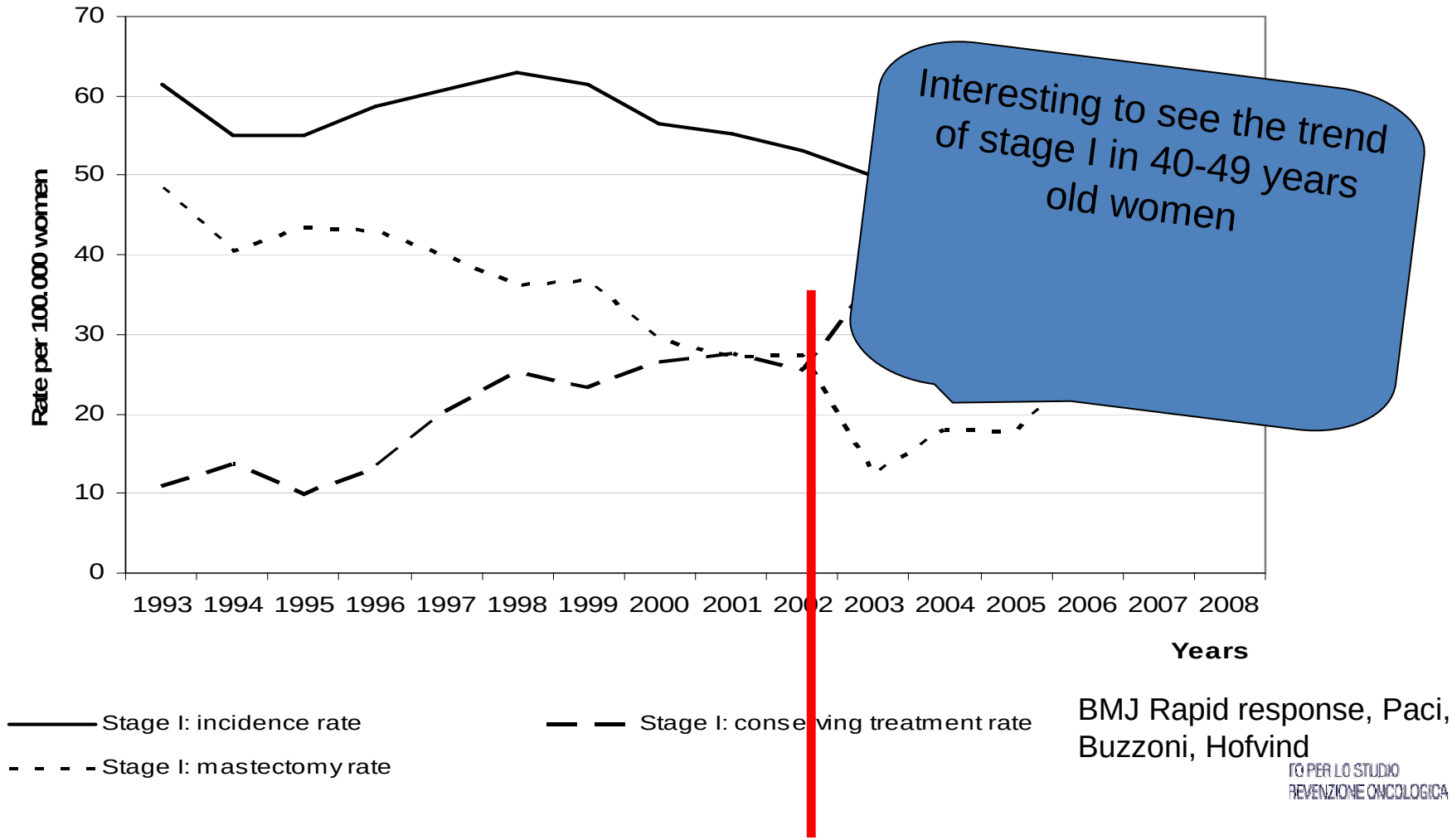
Pål Suhrke,[1] Jan Mæhlen,[1] Ellen Schlichting,[2] Karsten Juhl Jørgensen,[3] Peter C Gøtzsche,[3] Per-Henrik Zahl[4]

AGE SPECIFIC MASTECTOMY, BREAST SURGERY, AND INCIDENCE RATES IN NORWEGIAN WOMEN WITH INVASIVE BREAST CANCER OR DUCTAL CARCINOMA IN SITU



- Suhrke et al. concludes that mammographic screening is increasing the overall rates of breast surgery, and particularly the rate of mastectomies in the introduction phase of organized screening.
- Late and early breast cancer in the target population will be treated by breast conserving surgery (BCS) or mastectomy (excluding non operated). Guidelines suggest that breast cancer with a diameter of 30 mm of less should be offered breast conserving surgery.
-

Figure 1a. Norway. Female breast cancer, age: 40-49 years, stage I. Crude incidence rates and crude surgery rates



BMJ Rapid response, Paci, Buzzoni, Hofvind

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Figure 1b. Norway. Female breast cancer, age: 50-69 years, stage I. Crude incidence rates and crude surgery rates.

BMJ Rapid response, Paci, Buzzoni, Hofvind

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Problems in interpretation

- The issue of overdiagnosis should not be confused with the excess of incidence after start
- Increase in the incidence rate after the start of screening is needed, a marker of lead time, early indicator of efficacy
- The lead time is expressed by the decrease of breast cancer diameter, which is the major determinant of the use of breast conserving surgery
- The number of early stages , and total surgeries, must increase after the start of screening
- Rates of mastectomies decrease because of the decrease of diameter of the lesions and different surgeon's attitude towards BCS (30 mm)
- The real issue is professional culture, i.e. attitude towards BCS. This changed gradually everywhere in Europe , and service screening implementation contributed to this change.

Conclusions

- **Service screening is reducing deaths and adverse effects are in the range expected**
- **Informed choice in screening is an important value, but also the presentation of valid and clearly presented data**
- **Service screening has advantes in comparison with spontaneous screening, not only in terms of costs**
- **The conclusion of the EUROSCREEN working group is service screening should continue**
- **Concern for adverse effects is important as the achievement of the benefit(balance sheet)**
- **Research to reduce the burden of screening, improve informed choice and communication is needed**
- **Outcome research with methodological sound methodology is possible and it should be cooperative in Europe.**

- data for the choice is


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