

Riunione annuale screening mammografico Regione Veneto, 2010

*Le domande di fondo dello screening
mammografico: sintesi del dibattito
internazionale*

Eugenio Paci

Epidemiologia Clinica e Descrittiva



ISTITUTO PER LO STUDIO
E LA PREVENZIONE ONCOLOGICA

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

Va pensiero- Newsletter

13

How to... Le 5 cose importanti per lo screening mammografico

1 È ragionevole partecipare allo screening mammografico, ma è altrettanto ragionevole non parteciparvi

Lo screening ha contemporaneamente effetti positivi ed effetti negativi. Essi non sono di regola menzionati e nemmeno quantificati in modo comprensibile per la presa di decisione individuale sugli opuscoli ed i depliant di invito allo screening.

2 Quali i benefici?

Considerando 1000 donne di cinquanta e più anni di età che si sottopongono ogni due anni e per 10 anni allo screening mammografico il numero assoluto di donne che avranno evitato il decesso per tumore al seno sarà pari a 0,5 unità (visione "pessimista", 1) o al massimo a 2 unità (visione "ottimista", 2), rispetto a 1000 donne che non si sono sottoposte allo screening. Quindi 999,5 donne (rispettivamente 998) sulle 1000 che hanno partecipato allo screening non avranno nessun beneficio in termini di mortalità evitata.

3 Quali gli effetti negativi?

Sempre tra le 1000 donne citate che scelgono di sottoporsi allo screening, tra 2 e 10 riceveranno una diagnosi di forme pre-invasive di cancro al seno che non avrebbero causato dei sintomi o dei decessi nel corso della loro vita (sovra-diagnosi). Esse saranno quindi trattate inutilmente come se avessero un tumore al seno. Tra 10 e 15 donne avranno una diagnosi anticipata di cancro senza che questo fatto abbia un'influenza sulla prognosi, infine tra 100 e 500 donne sperimenteranno dei falsi allarmi (falsi positivi) che per circa il 50% daranno luogo ad un'ulteriore mammografia. Inoltre 5 donne saranno falsamente rassicurate dal screening mammografico (falsi negativi).

4 Screening mammografico: un delicato bilancio

Partecipare o non partecipare allo screening mammografico significa operare a **livello individuale** un delicato bilancio tra benefici ed effetti negativi e quindi le scelte possono essere ragionevoli sia a favore che contro la partecipazione ad un programma di screening (4).

5 Evitare e rifiutare la propaganda

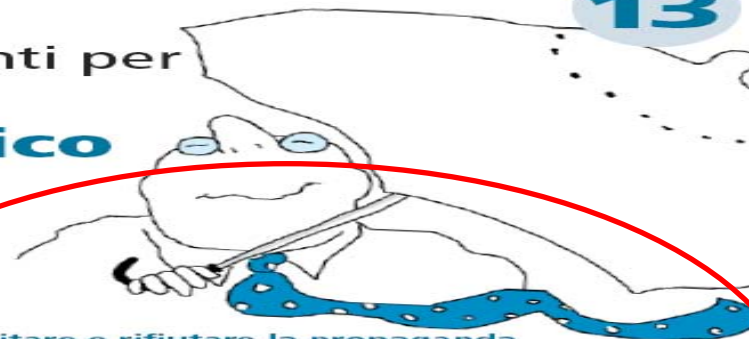
Oggi giorno i contenuti della quasi totalità degli opuscoli, dei depliant e delle lettere di invito allo screening mammografico tutti silenti sulla elencazione e sulla quantificazione dei benefici e degli effetti negativi, non promuovono l'autonomia ad operare delle scelte individuali bensì essi non costituiscono che della propaganda. Il materiale informativo non dovrebbe essere redatto dai promotori dello screening (per evidenti motivi di conflitto di interesse) bensì da agenzie neutre sulla base dei più rigorosi criteri scientifici (5). Due opuscoli, uno danese (in inglese) e l'altro svizzero (in lingua italiana) rispondono in modo soddisfacente a questi criteri (6,7).

Gianfranco Domenighetti

Professore di Comunicazione, Economia e Politica sanitaria Università della Svizzera Italiana e di Losanna

Note dell'autore

1. Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev 2006; 4:CD001877
2. Barrat A, Howard K, Irwig L, et al. Model of outcomes of screening mammography: information to support informed choices. BMJ 2005; 330: 936-8.
3. Welch G. Overdiagnosis and mammography screening. BMJ 2009;339: b1425
4. Heath I. It is not wrong to say no. BMJ 2009; 338: b2529
5. Agency for Healthcare Research and Quality. Breast cancer screening. Summary of the evidence <http://www.ahrq.gov/clinic/3rduspstf/breastcancer/bcscrnsum1.htm#results>
6. www.screening.dk
7. La mammografia: un aiuto per capire e per decidere. Opuscolo del Dipartimento della sanità e della socialità, Bellinzona 2008. www.ti.ch/dss/dsp/sezs/UffPVS/progetti/Diritto_dei_pazienti/pdf/OpuscoloMammografia.pdf



Comunicare si, ma che cosa?

- E' corretto che una posizione che diviene autorevole perché è ospitata sui principali media scientifici internazionali, ma è considerata da molti come metodologicamente e scientificamente insostenibile , sia considerata il vero messaggio da comunicare?
- Un buon numero di ricercatori ritiene le stime del gruppo Gotschtze (Cochrane?) inaccurate e sbagliate: è giusto informare , ma come si informa su una questione così controversa ?

Scenario and Contents of the balance sheet

	Welch, NEJM 2010	Welch, JNCI 2010	Duffy, J Med Screen 2010	Gotzsche, BMJ 2009	Florence, <i>in progress</i>
Scenario	2500 50-year-old women screened every year for 10 years	1000 50-year-old women screened every year for 10 years	1000 50-years-old women screened every two years for 20 years	2000 50-years-old women screened every two years for 10 years	1000 50-year-old women screened every two years for 20 years and followed until 79 years old
Contents of benefits and harms	Benefit: Reduction in mortality Harm: 1. Overdiagnosis 2. False positive	Benefit: a) Reduction in mortality Harm: b1) Overdiagnosis b2) The useless advance knowledge of BC b3) False positive	Benefit: Reduction in mortality Harm: Overdiagnosis	Benefit: Reduction in mortality Harm: 1. Overdiagnosis 2. False positive	Benefit: Reduction in mortality Harm: 1. Overdiagnosis 2. False positive
Measures of benefits and harms	Absolute number of: a) lives saved b) healthy women experienced an harm (cancer diagnosis, false alarm)	Absolute number of: a) lives saved b) healthy women experienced an harm (cancer diagnosis, poorer quality of life, false alarm)	Absolute number of: a) lives saved b) healthy women experienced an harm (cancer diagnosis)	Absolute number of: a) lives saved b) healthy women experienced an harm (cancer diagnosis, false alarm)	Absolute number of: a) lives saved b) healthy women experienced an harm (cancer diagnosis, false alarm)
TRADE-OFF: N° overdiagnosed cases for every life saved	5-15	2-10	0.4-0.5	10	0.75

DEFINIZIONE

- **La proporzione di casi di cancro confermati istologicamente e diagnosticati a seguito di un episodio di screening che non sarebbero giunti all'attenzione clinica se non fosse stato eseguito.**

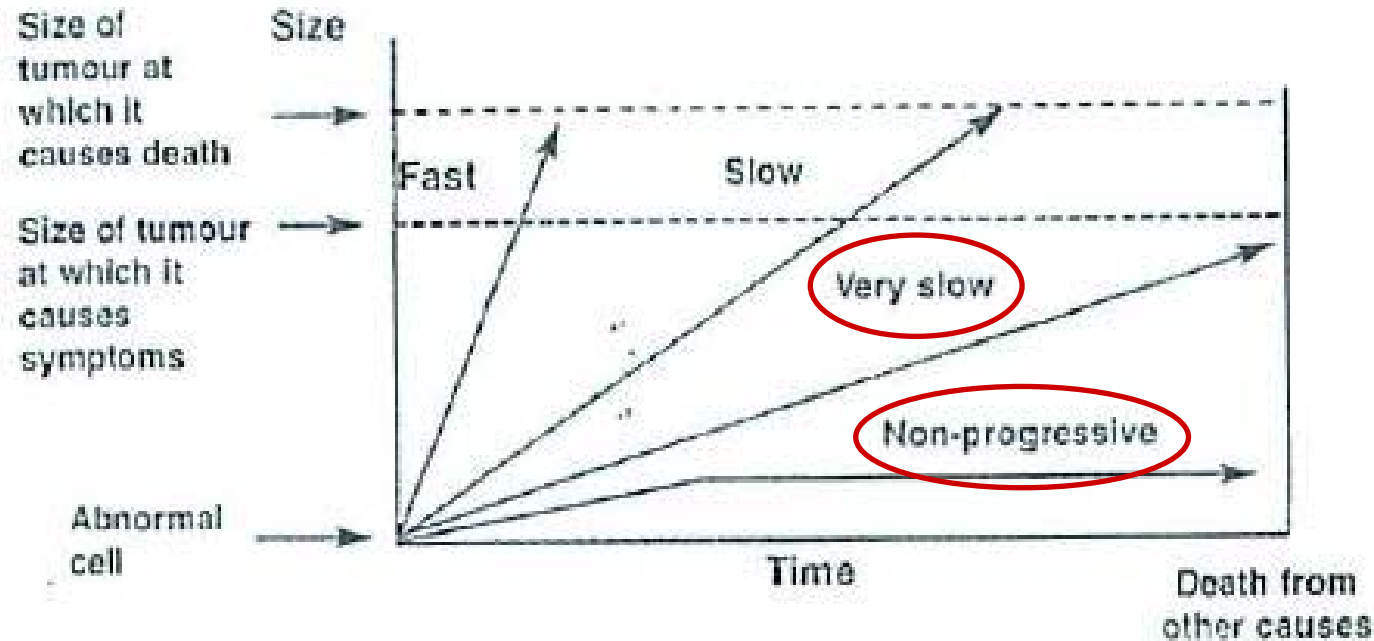
Sovradiagnosi e tumore della mammella

“

E' una combinazione di cause (e può essere considerata da diverse prospettive)

- 1) La storia naturale della malattia (basso o nessun potenziale di progressione a malattia sintomatica
- 2) la storia epidemiologica , funzione della durata di vita della donna o di rischi competitivi di morte per altre cause)

Growth rates of cancers (IARC, 2002)



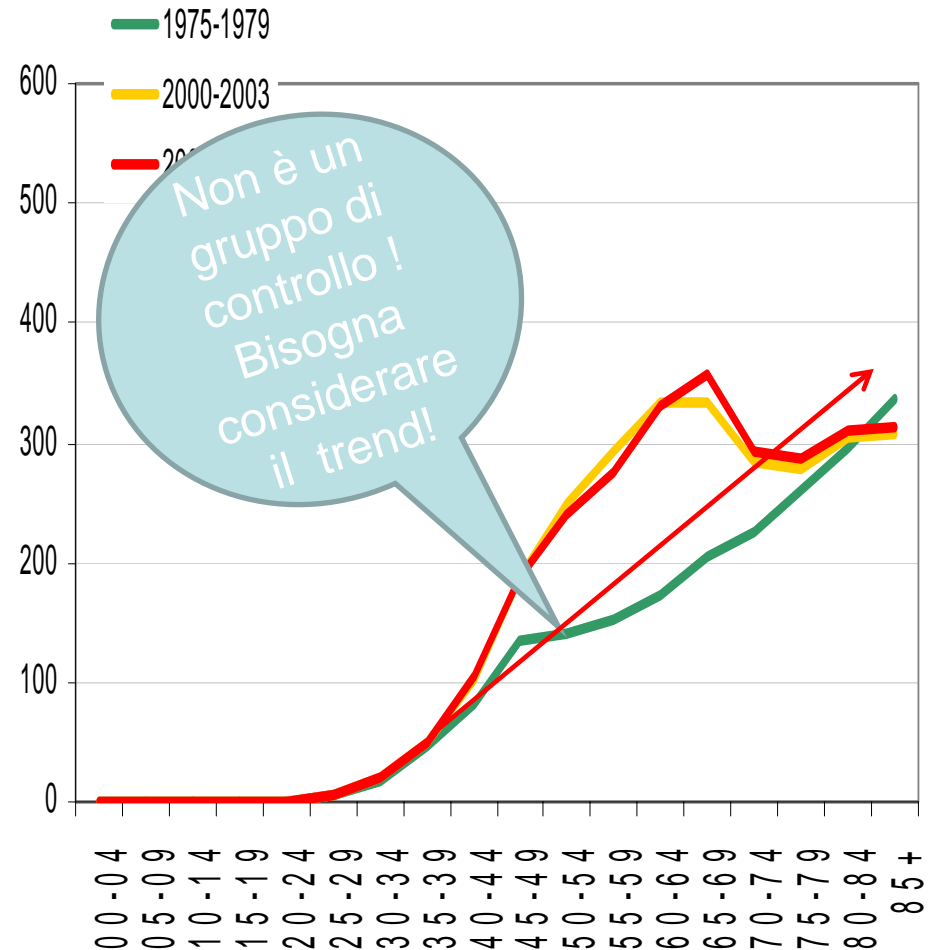
The diagnosis of these cancers (very slow and non-progressive), that Morrison (1975) have called "pseudodisease", is overdiagnosis.

Il tempo

1. Lo screening funziona perchè anticipa la diagnosi , quindi un eccesso di incidenza dopo l'inizio di un programma di screening è non solo atteso , ma anche voluto (Lead time)
2. Solo i casi identificati allo screening possono avere un beneficio. Occorrono molti anni per garantire la copertura della popolazione, e essa è funzione della sensibilità (casi di intervallo) e della partecipazione (non rispondenti)

FIGURE 1B. Breast cancer. Incidence rates by age and period
NORDCAN-Nordic countries (EU)

- Con l'avvio del programma di screening (50-69 anni) si verifica un aumento dei casi di malattia.
- Questo eccesso di incidenza continua se lo screening continua
- Se lo screening si interrompe (69 anni) la probabilità di ammalare nel corso di una vita per una donna dovrebbe essere uguale a quella in assenza di screening.
- La diagnosi che persiste nel tempo, diagnosi futile, è la sovradiagnosi



Estimates of overdiagnosis with cumulative-incidence method

Study	Type of study	Country	Age at entry	N° invitations	Years of follow-up*	Estimate of overdiagnosis
Miller, 2002	Canadian trial I	Canada	40-49	5 annual	5	14%
Miller, 2002	Canadian trial II	Canada	50-59	5 annual	5	11%
Zackrisson, 2006	Malmo trial	Sweden	55-69	7 biennial	15	10%
Puliti, 2009	Observational	Italy	60-69	3 biennial	7	1-13%
Florence, in progress	Observational	Italy	60-69	3 biennial	10	10%

(*) Years of follow-up after screening ends

Notes:

Measure = BC cases among Invited / BC cases among Not-invited

All estimates are referred to all breast cancers (invasive and insitu)

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

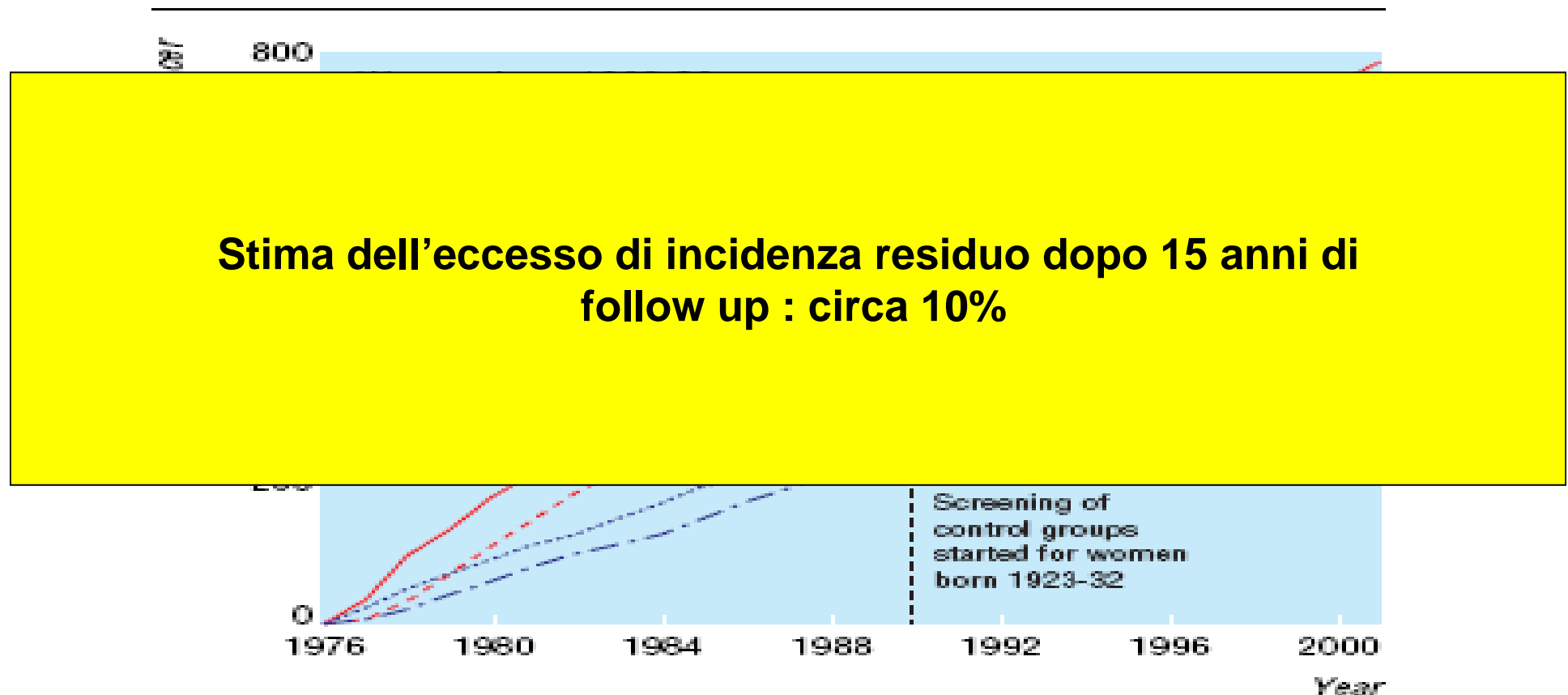


Fig 2 Cumulative number of all breast cancer cases (in situ and invasive) per year and group for total follow-up of women born during 1908-22 (unscreened control group) and 1923-32 (controls groups invited to screening from 1990 onwards.)

Estimates with statistical methods to adjust for lead-time

- Incidence shifted (forward or backward?) to take into account the lead time

Authors	Country	Expected incidence	Observed incidence	Lead time	Estimate of overdiagnosis
Paci, 2004	Italy	pre-screening incidence	corrected for lead time	Exponential distribution	5%
Paci, 2006	Italy	expected incidence (annual trend)	corrected for lead time	Exponential distribution	5%
Morrell, 2009	Australia	expected corrected for lead time	screening incidence	Average	30-42%

Authors	Country	Expected incidence	Observed incidence	Lead time	Excess risk adj for lead time
Jonsson, 2005	Sweden	expected incidence (annual trend)	corrected for lead time	Average x % screen-detected	21-54%

Estimates with statistical methods to adjust for lead-time

- Compensatory drop in incidence above the age limits for screening, microsimulations, fitting multistate models to the screening data, etc..

Authors	Study design	Country	Method	Estimate of overdiagnosis
Zahl, 2004	Observational study	Norway, Sweden	compensatory drop	33%
de Koning, 2005	Microsimulation model	The Netherland	modelling	3%
Duffy, 2005	Two County and Gothenburg trial	Sweden	multistate modelling	2%
Olsen, 2006	Observational study	Denmark	multistate modelling	5%
Jorgensen, 2009	Observational study	5 countries	compensatory drop	52%
Jorgensen, 2009	Observational study	Denmark	compensatory drop	33%
Duffy, 2010	Observational study	UK	compensatory drop	4%
Duffy, 2010	Two County trial	Sweden	modelling	9%

1) The cohort of women 50-69 years old at the beginning of service screening

EUROPEAN JOURNAL OF CANCER 45 (2009) 3166–3171



available at www.sciencedirect.com



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

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.

Method: Cumulative incidence method.

Measure: The measure of overdiagnosis is the ratio of cumulative incidence of breast cancers in the invited group at least 5 years after the last screen to that in the non-invited group.

"Invited" group (observed):

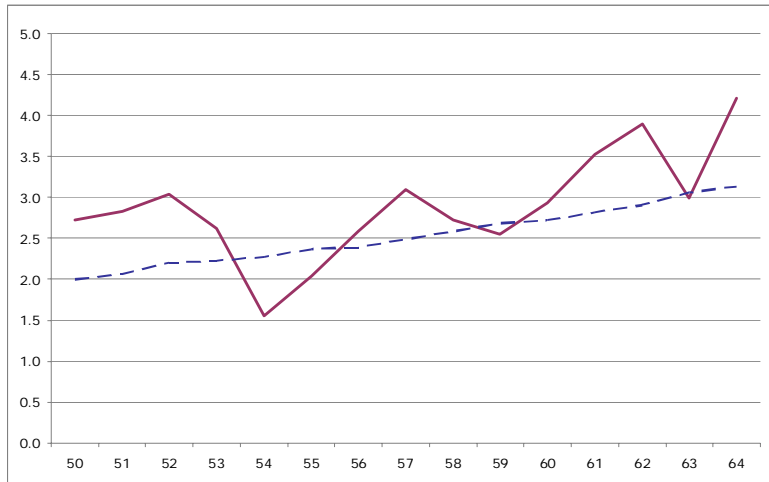
Cohort of women aged 50-69 at the beginning of service screening (61,568 women) and follow up for breast cancer incidence between 1991 and 2004.

"Non-invited" group (expected):

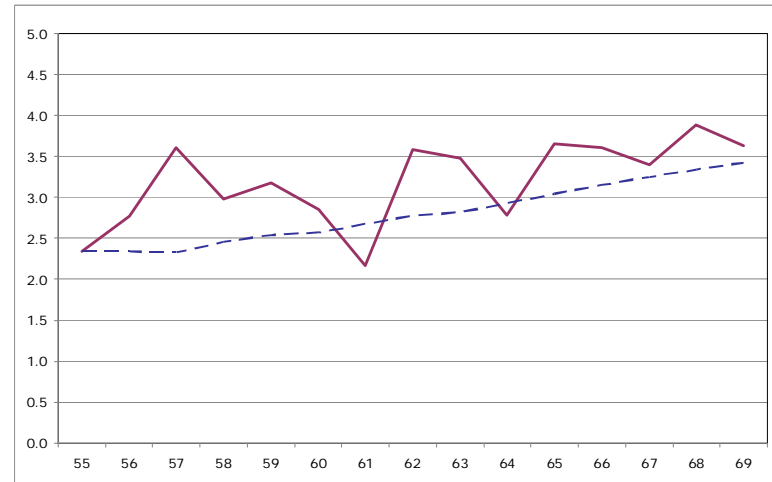
A Poisson regression model (with age and calendar year) was fitted to Florentine pre-screening incidence data (1986-1990) and the annual trend was forced to 1.2% (pooled estimate in North-Central Italy).

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

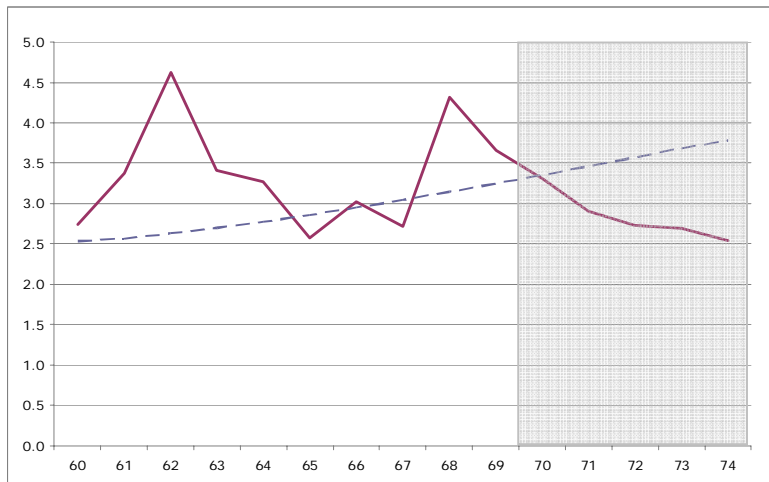
a) 50-54 years



b) 55-59 years



c) 60-64 years



d) 65-69 years

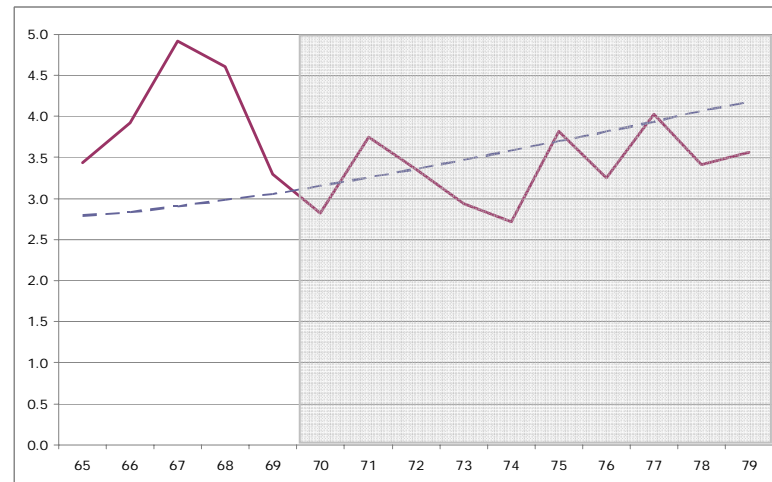
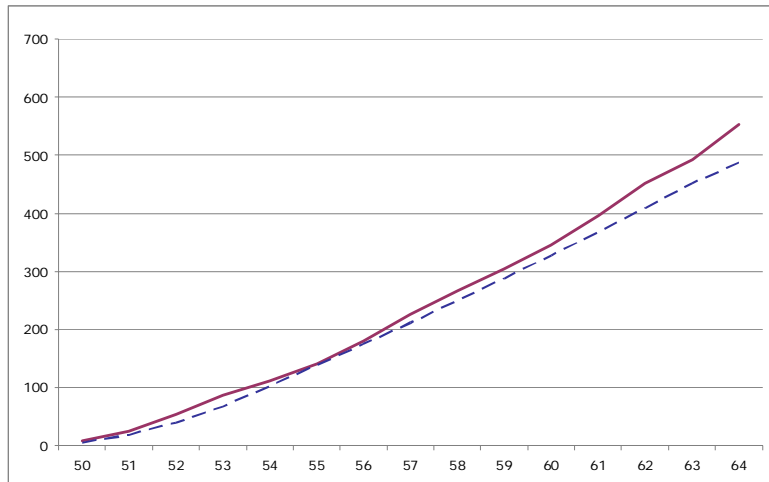
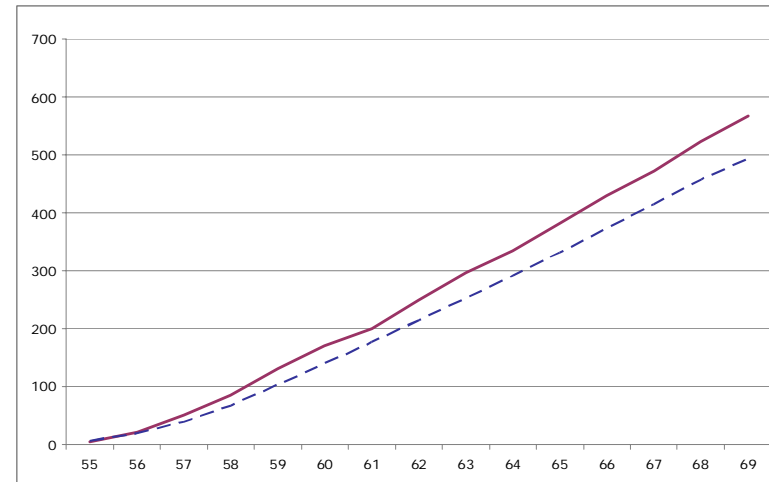


FIGURE 2. Invited (observed) and non-invited (expected) cumulative breast cancer cases by age at the beginning of service screening:

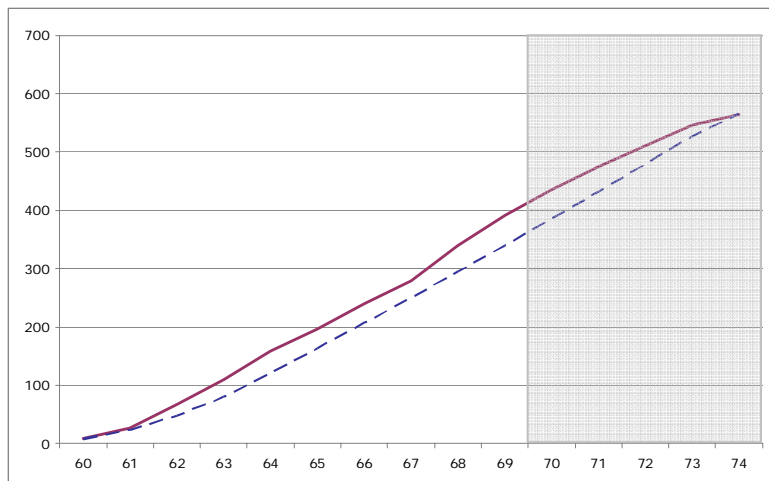
a) 50- 54 years



b) 55-59 years



c) 60-64 years



d) 65-69 years

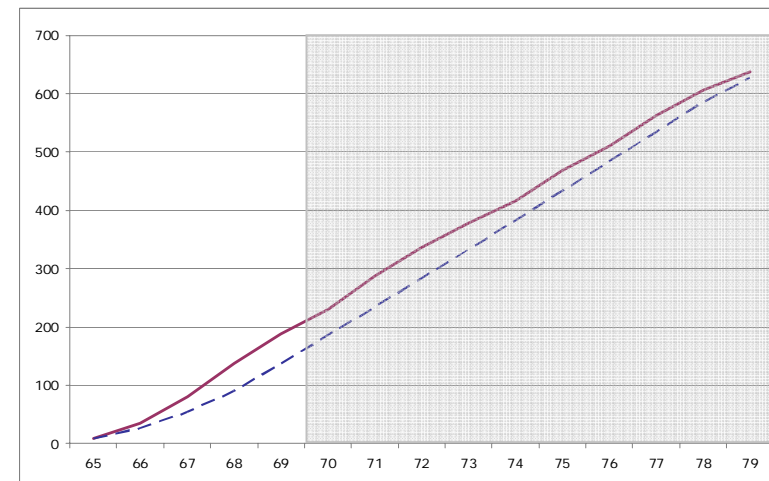
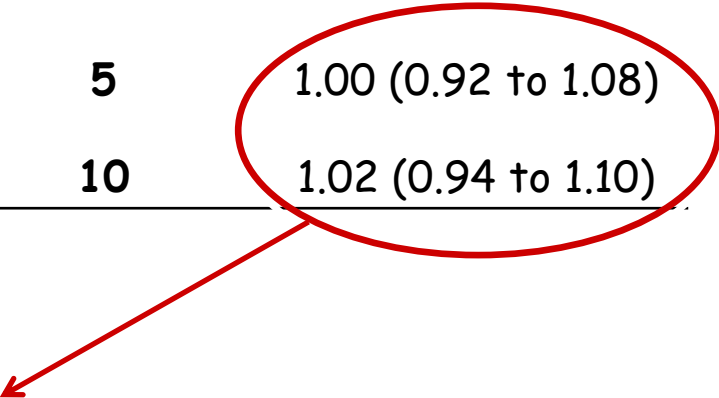


TABELLA 1.

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	1.14 (1.04 to 1.23)	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	1.00 (0.92 to 1.08)
65-69	5	1.36 (1.17 to 1.57)	10	1.02 (0.94 to 1.10)

1.01 (0.95 - 1.07)
for in situ and invasive cases



Sensitivity analysis

In order to assess how our estimate of overdiagnosis depends upon pre-screening trend estimates, we performed a sensitivity analysis assuming the most extreme scenario: **the absence of incidence trend.**

In this case, the estimate of overdiagnosis for women 60-69 years at the enrolment was **1.13 (1.07 - 1.19).**

Zahl et al : quantificazione della sovradiagnosi in studi descrittivi

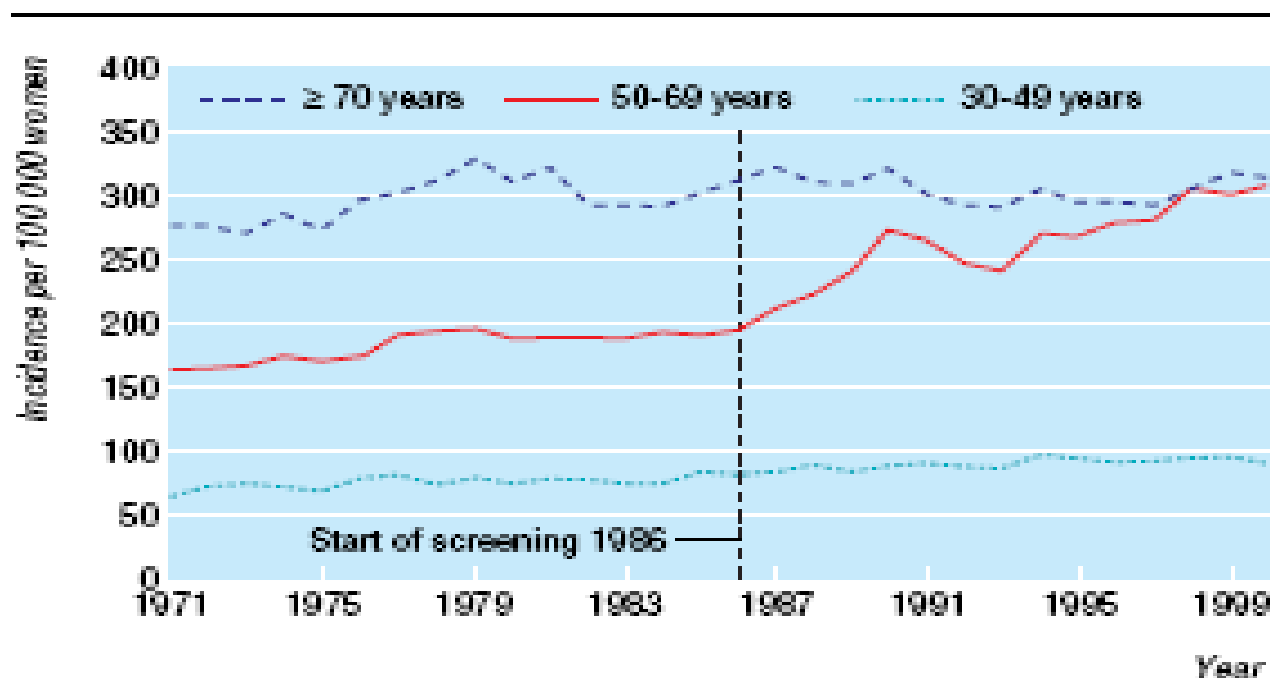


Fig 2 Age-specific incidence of invasive breast cancer in Sweden and for age groups 30-49, 50-69, and >69 years. Vertical line indicates start of organised screening in Sweden (1986)

Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study

Per-Henrik Zahl, Bjørn Heine Strand, Jan Mæhlen

What is already known on this topic

Nationwide mammography screening results in a substantial increase in the reported incidence of invasive breast cancer in the invited population

It was expected that most of this increase would be compensated for by falling incidence rates when the women are no longer invited for screening

What this study adds

In Norway and Sweden the increase in incidence related to screening in the invited population has not been followed by a similar fall in incidence at later ages

The level of overdiagnosis in nationwide mammography screening is much higher than previously thought

Table 2 Estimated relative risks of breast cancer (excluding ductal carcinoma in situ) in Sweden

	RR (95% CI)
1971 (reference)	1.0
Annual increase:	
1972-85	1.008 (1.007 to 1.009)
1986-2000	1.001 (0.998 to 1.003)
Age 50-69 years:	
1986-9	1.06 (1.03 to 1.09)
1990-3	1.31 (1.28 to 1.34)
1994-6	1.28 (1.25 to 1.32)
1997-2000	1.45 (1.41 to 1.49)
Age 70-74 years:	
1994-6	0.98 (0.93 to 1.03)
1997-2000	1.01 (0.96 to 1.05)
Age 75-79 years:	
1997-2000	0.88 (0.84 to 0.92)

BMI

RESEARCH

◀ **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.

before screening and seven years after screening had 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.³⁴

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.⁵⁶ The total number of mastectomies and lumpectomies increased by 31%

implement screening. We reasoned that a long period after implementation was necessary to obtain an estimate of the trend in breast cancer incidence that was unaffected by the initial peak in prevalence when screening is introduced. Acquiring incidence data for age groups older than those screened allowed us to evaluate any compensatory declines in incidence among previously screened women.

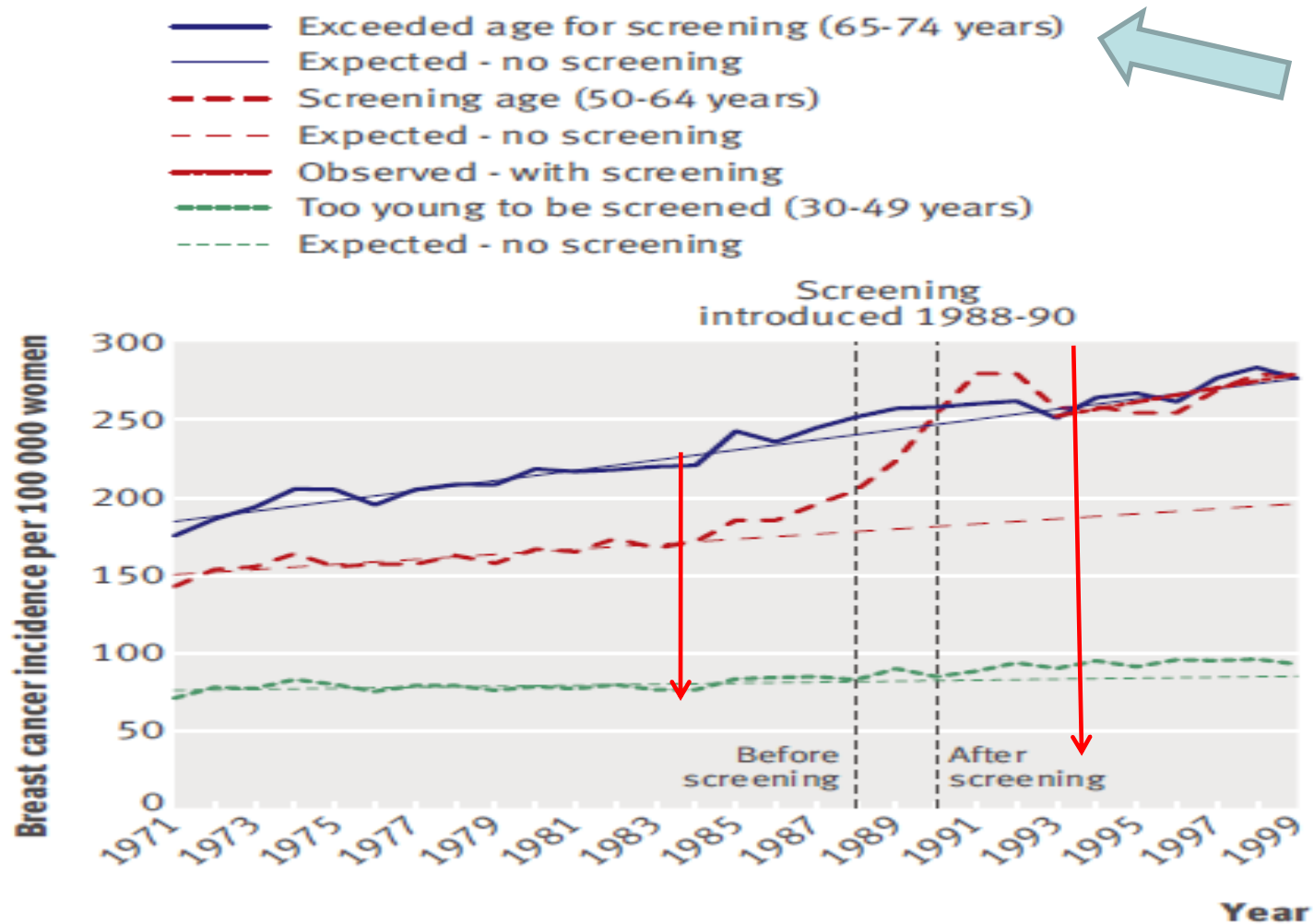
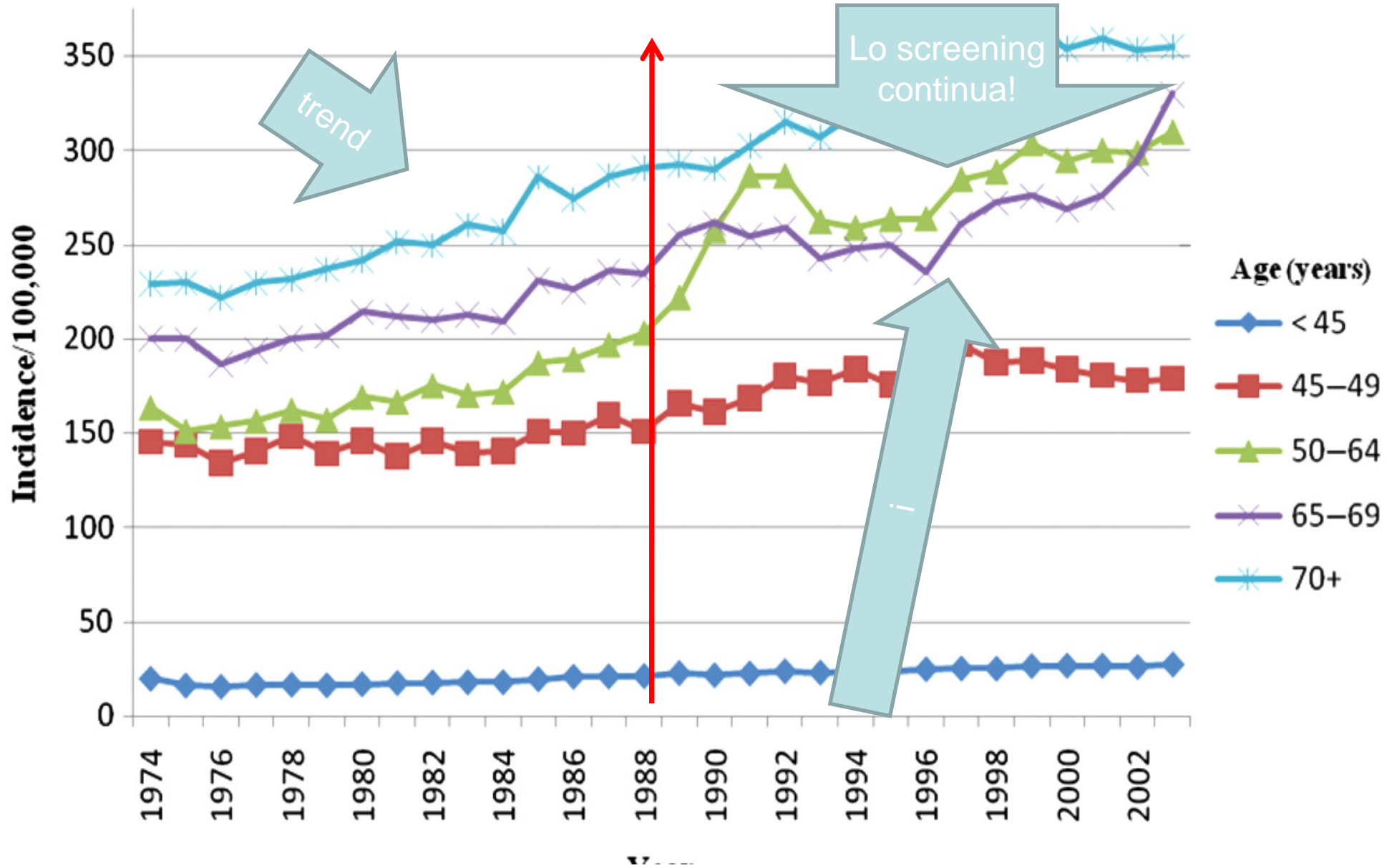


Fig 2 | Incidence of invasive breast cancer per 100 000 women in UK

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



Eccesso di incidenza e Lead time

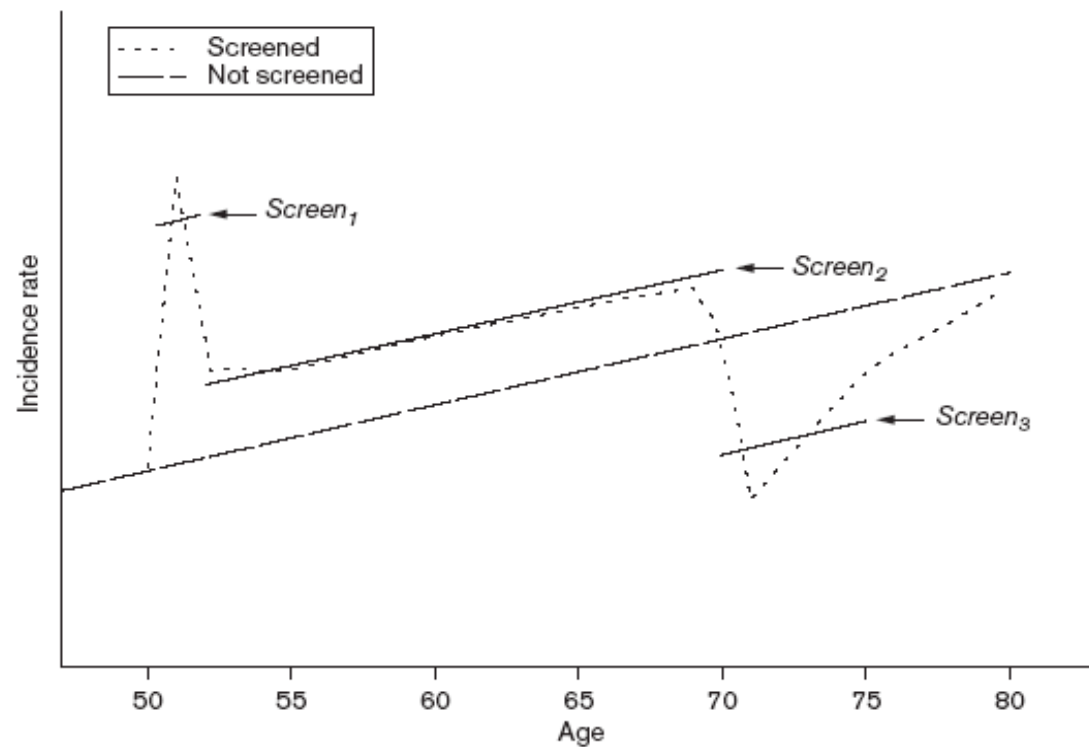
- Non si deve confondere l'eccesso di incidenza , che è necessario perché lo screening funzioni , con la sovradiagnosi
- L'eccesso di incidenza permane fintanto che persiste lo screening (organizzato o spontaneo)
- Il riassorbimento non può essere valutato in studi descrittivi se non dopo molti anni dall'inizio dello screening. E' studiabile con approcci coorte o con modelli che considerino il lead time.

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

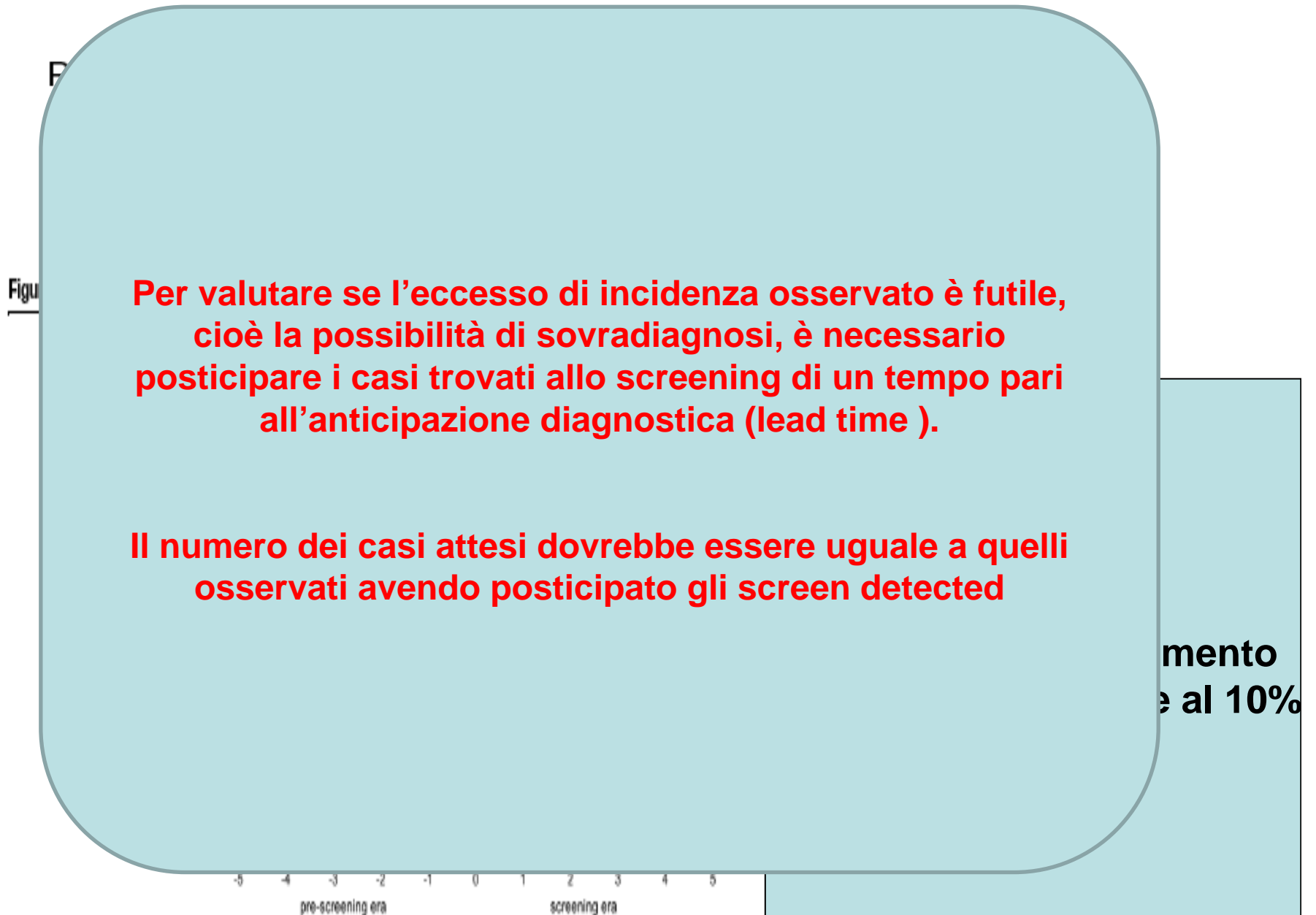
B Møller¹, H Weedon-Fekjær¹, T Hakulinen², L Tryggvadóttir³,
H H Storm⁴, M Talbäck⁵ and T Haldorsen¹

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. *Screen₁*, *screen₂* and *screen₃* are the effects of the initial screening round, subsequent screening rounds, and post screening, respectively.

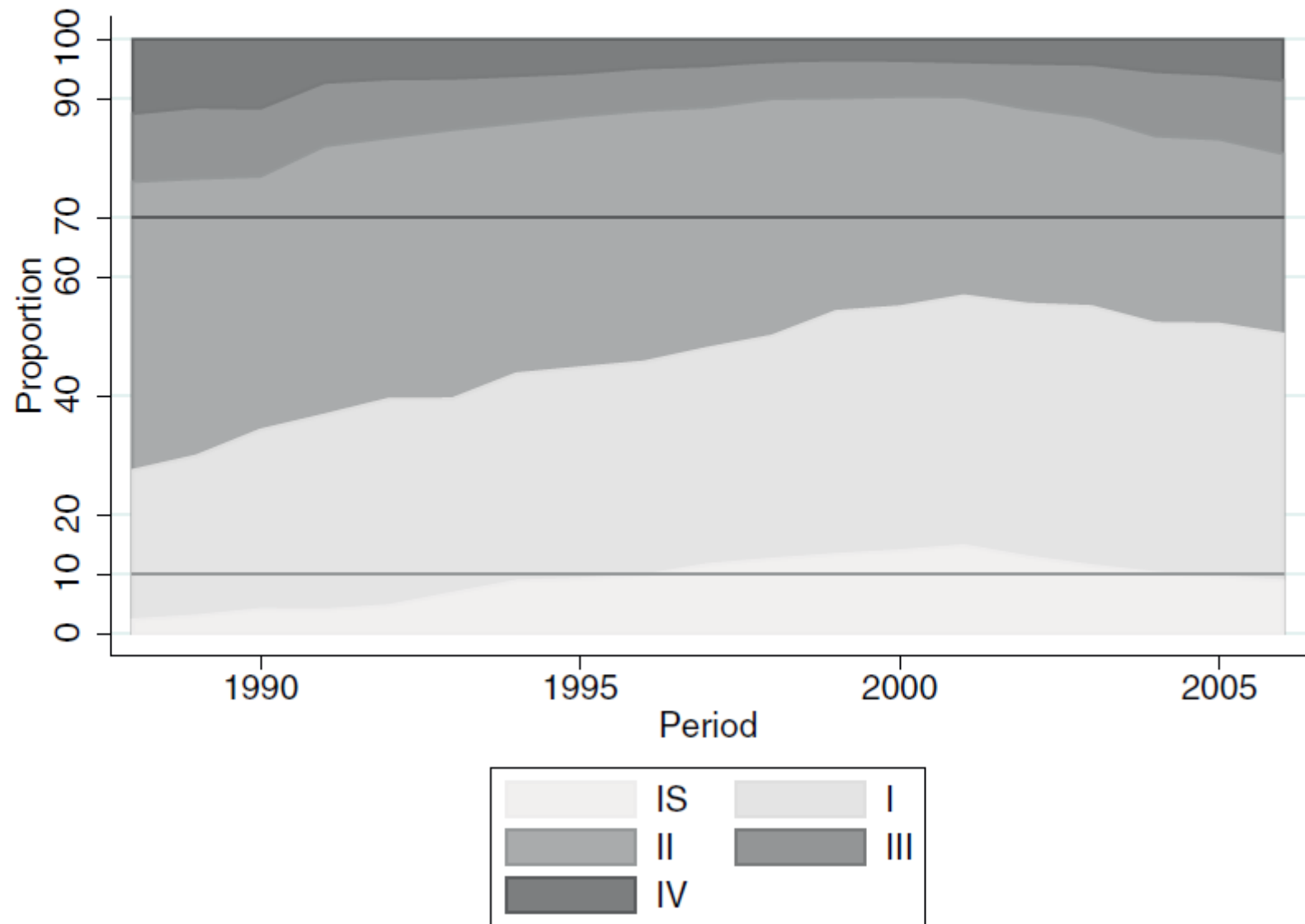


Lo screening spontaneo e lo screening organizzato

- Lo screening organizzato aggiunge il suo impatto a quello dello screening spontaneo , forse con diversa sensibilità , specificità, sovradiagnosi e efficacia
- Lo screening spontaneo è raramente valutato, ma è ipotizzabile un effetto sull'incidenza e mortalità negli anni 90. .

Breast cancer incidence and mortality in Tyrol/ Austria after fifteen years of opportunistic mammography screening

Willi Oberaigner^{1,2,3*}, Wolfgang Buchberger^{2,4†}, Thomas Frede^{5†}, Rudolf Knapp^{6†}, Christian Marth^{7†},
Uwe Siebert^{2,3,8,9†}



Problemi principali

- **Quantificazione della sovradiagnosi (in parte è inevitabile per caratteristiche proprie di una iniziativa di anticipazione diagnostica)**
- **Valutazione del suo impatto in rapporto al conseguente sovratrattamento**
- **Valutazione di cost/ effectiveness**
- **Implicazione per le decisioni informate**

BILANCIO DEI BENEFICI E DEI POTENZIALI DANNI DI UN PROGRAMMA DI SCREENING

Beneficio: riduzione della mortalità per TM = 25% (Puliti D et al, 2008)

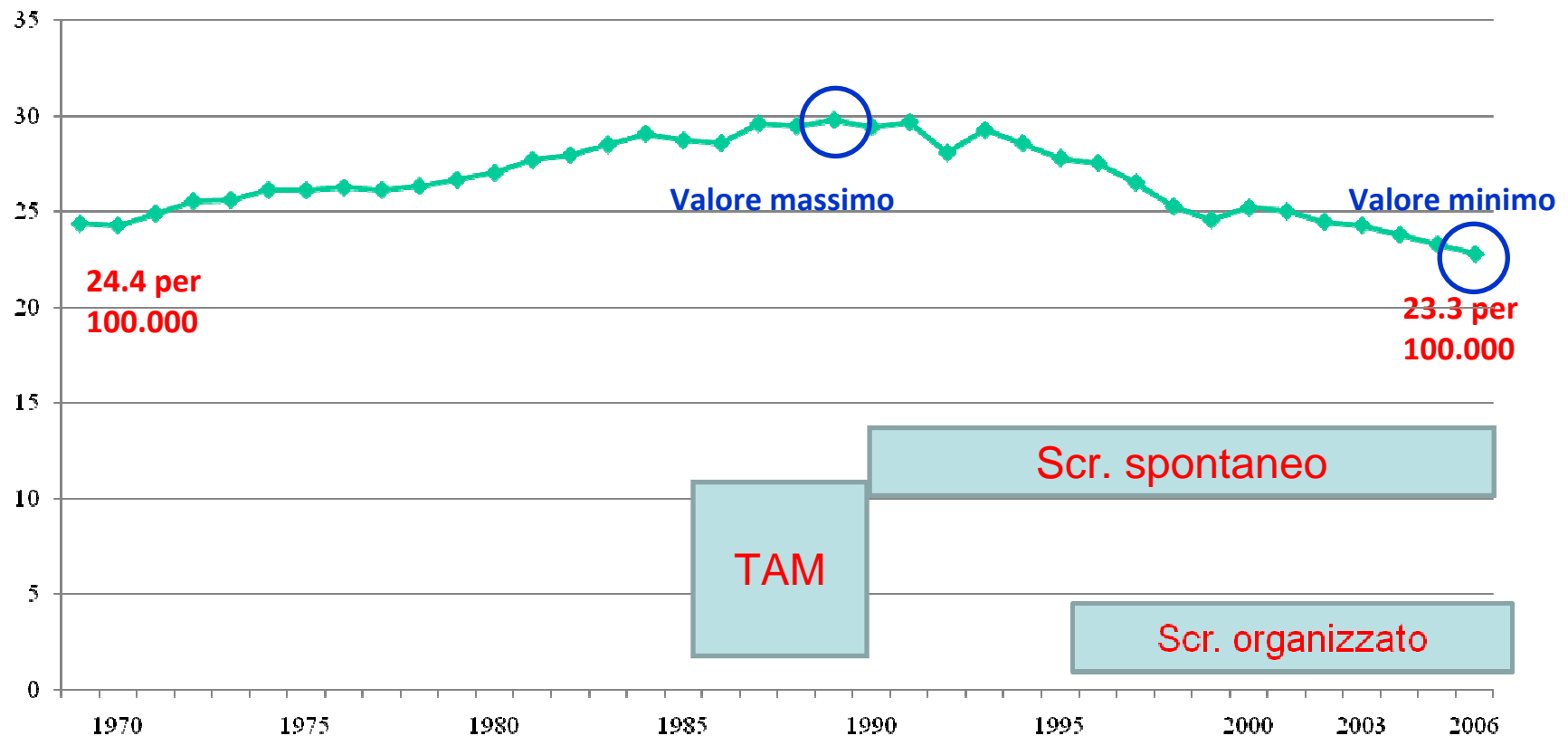
Danno: overdiagnosi = 1% (best evidence) - 13% (no trend)

In una popolazione dove il rischio di sviluppare un tumore alla mammella tra i 50 ed i 79 anni è del 6.5% ed il rischio di morire per tumore della mammella nella stessa classe di età è del 2.5%, invitare allo screening 1000 donne:

- può prevenire 6 morti per tumore della mammella su 25 morti attese
- ma potrebbe condurre alla sovradiagnosi, nel peggior e più improbabile scenario, fino ad un massimo di 8 casi su 65 casi in situ ed invasivi attesi.

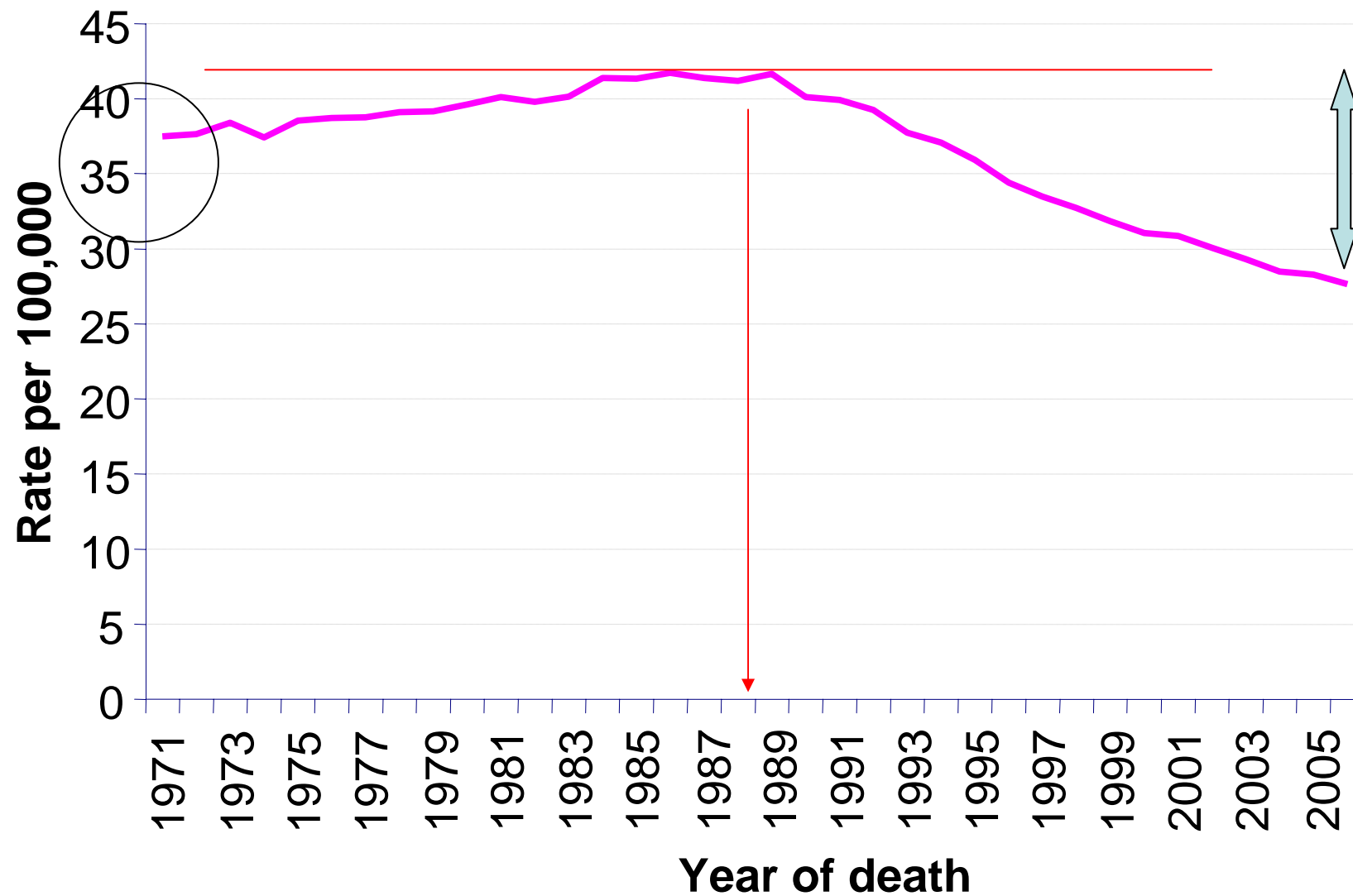
Tassi standardizzati di mortalità per tumore della mammella

(Italia 0-99 anni) –ISS ISTAT IMPATTO



Tassi standardizzati * 100.000 - Popolazione standard: Europa

Age-standardised (European) mortality rates, breast Breast cancer , females, UK 1971-2006



Galleria degli Uffizi



Lo scelta informata , basato sui dati dei programmi di screening Italiani

- **In uno scenario di 20 anni , che è quello più convincente , vi sarebbero 9 donne salvate dall'essersi sottoposte allo screening a confronto con 19 decessi attesi per tumore della mammella in assenza di partecipazione allo screening ogni 1000 donne screenate.**
- **Nota:studio caso controllo, Progetto Impatto, BJC, 2008**

Results A substantial and significant reduction in breast cancer mortality was associated with screening in both the Two-County Trial ($P < 0.001$) and the screening programme in England ($P < 0.001$). The absolute benefits were estimated as 8.8 and 5.7 breast cancer deaths prevented per 1000 women screened for 20 years starting at age 50 from the Two-County Trial and screening programme in England, respectively. The corresponding estimated numbers of cases overdiagnosed per 1000 women screened for 20 years were, respectively, 4.3 and 2.3 per 1000.

Conclusions The benefit of mammographic screening in terms of lives saved is greater in absolute terms than the harm in terms of overdiagnosis. Between 2 and 2.5 lives are saved for every overdiagnosed case.

Conclusione

- Sulla base dei dati pubblicati dallo studio randomizzato di Malmo la stima è del 10%, con un numero atteso di 4 casi sovradiagnosticati quando 1000 donne sottoposte a screening sono seguite per venti anni , l'usuale finestra temporale utilizzata per valutare lo screening.
- Circa 0.5 casi sovradiagnosticati per ogni morte risparmiata
- Una stima confermata dal recente lavoro sui dati UK S.Duffy et al, JMS, 2010

Lo scelta informata , basato sui dati dei programmi di screening Italiani

- **In uno scenario di 20 anni , che è quello più convincente , vi sarebbero 9 donne salvate dall'essersi sottoposte allo screening a confronto con 19 decessi attesi per tumore della mammella in assenza di partecipazione allo screening ogni 1000 donne screenate.**
- **Nota:studio caso controllo, Progeto Impatto, BJC, 2008**

Results A substantial and significant reduction in breast cancer mortality was associated with screening in both the Two-County Trial ($P < 0.001$) and the screening programme in England ($P < 0.001$). The absolute benefits were estimated as 8.8 and 5.7 breast cancer deaths prevented per 1000 women screened for 20 years starting at age 50 from the Two-County Trial and screening programme in England, respectively. The corresponding estimated numbers of cases overdiagnosed per 1000 women screened for 20 years were, respectively, 4.3 and 2.3 per 1000.

Conclusions The benefit of mammographic screening in terms of lives saved is greater in absolute terms than the harm in terms of overdiagnosis. Between 2 and 2.5 lives are saved for every overdiagnosed case.

Conclusione

- Sulla base dei dati pubblicati dallo studio randomizzato di Malmo la stima è del 10%, con un numero atteso di 4 casi sovradiagnosticati quando 1000 donne sottoposte a screening sono seguite per venti anni , l'usuale finestra temporale utilizzata per valutare lo screening.
- Circa 0.5 casi sovradiagnosticati per ogni morte risparmiata
- Una stima confermata dal recente lavoro sui dati UK S.Duffy et al, JMS, 2010