

# Storia dello screening mammografico



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**Screening  
mammografico:  
impronte,  
traiettorie,  
percorsi**

Alfonso Frigerio







# Storia dello screening mammografico

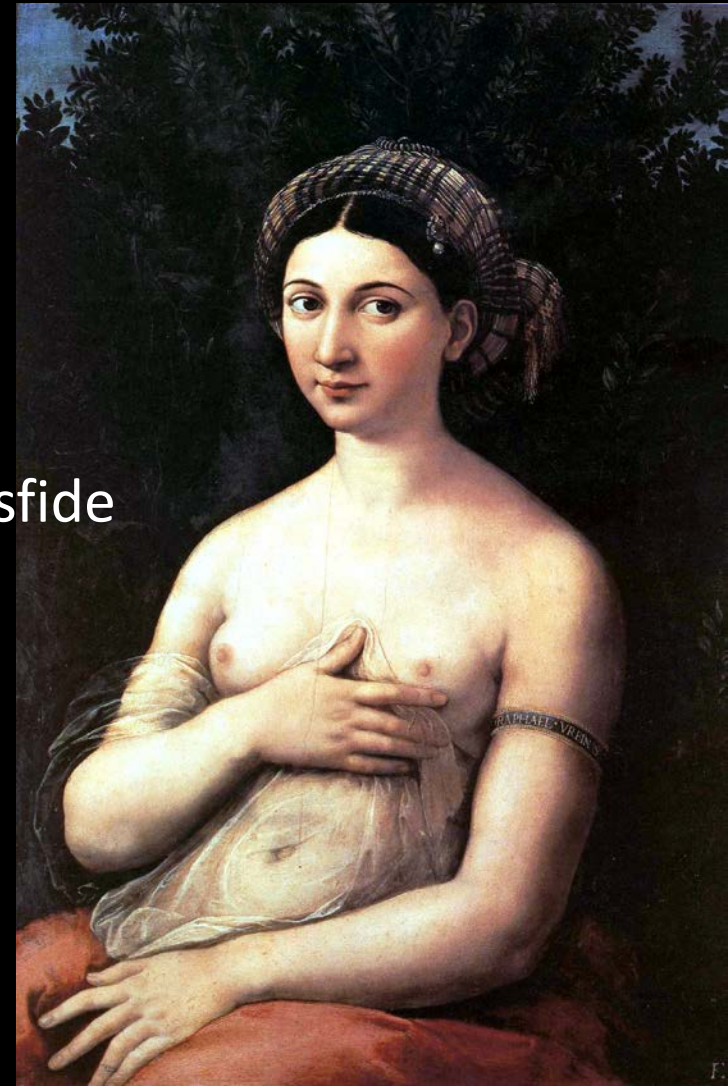
Conflitti di interesse /  
rapporti di finanziamento con aziende:  
nessuno

Alfonso Frigerio



# Storia dello screening mammografico / temi

- Storia del cancro mammario
- Le prove di efficacia dello screening
- La diffusione dello screening
- Le polemiche sullo screening
- La nuova era dello screening: successi e sfide





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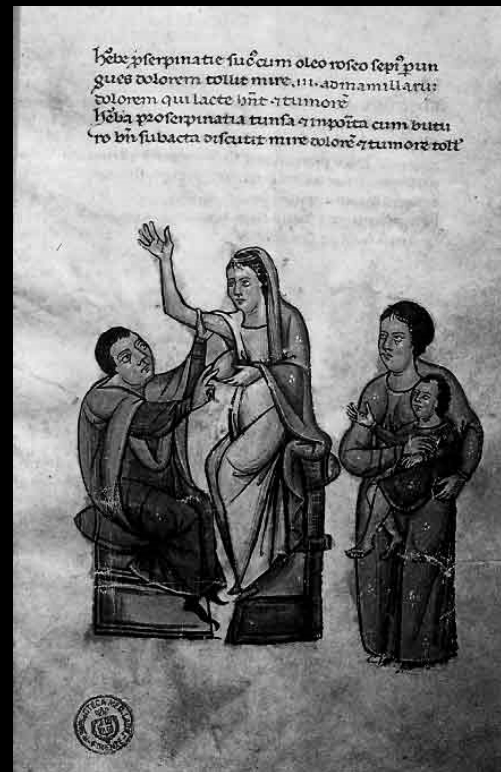
# Storia del cancro mammario

## Una malattia antica



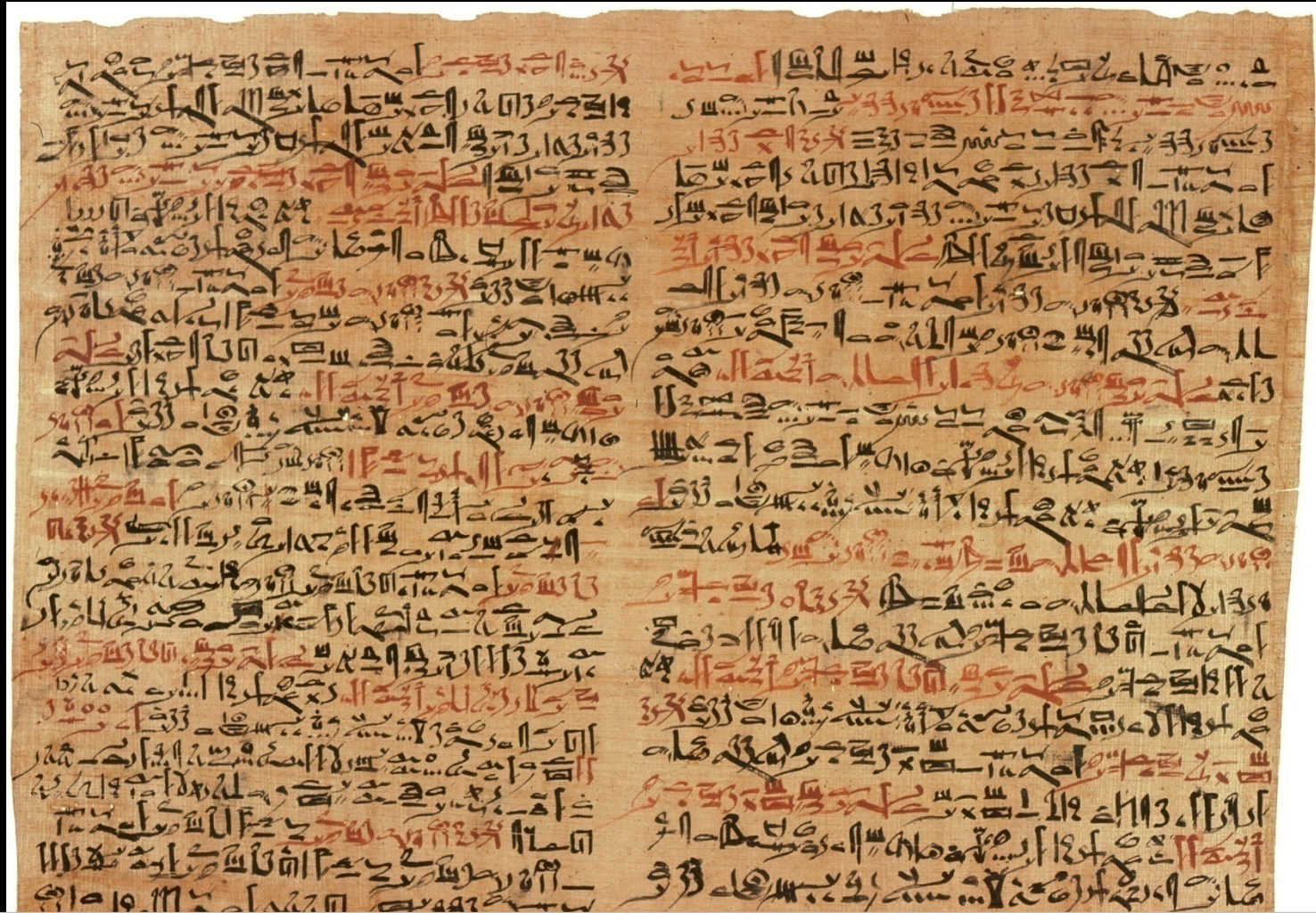


# cancro mammario / malattia antica





# cancro mammario / malattia antica



La prima segnalazione di un cancro mammario  
3000 a.C.



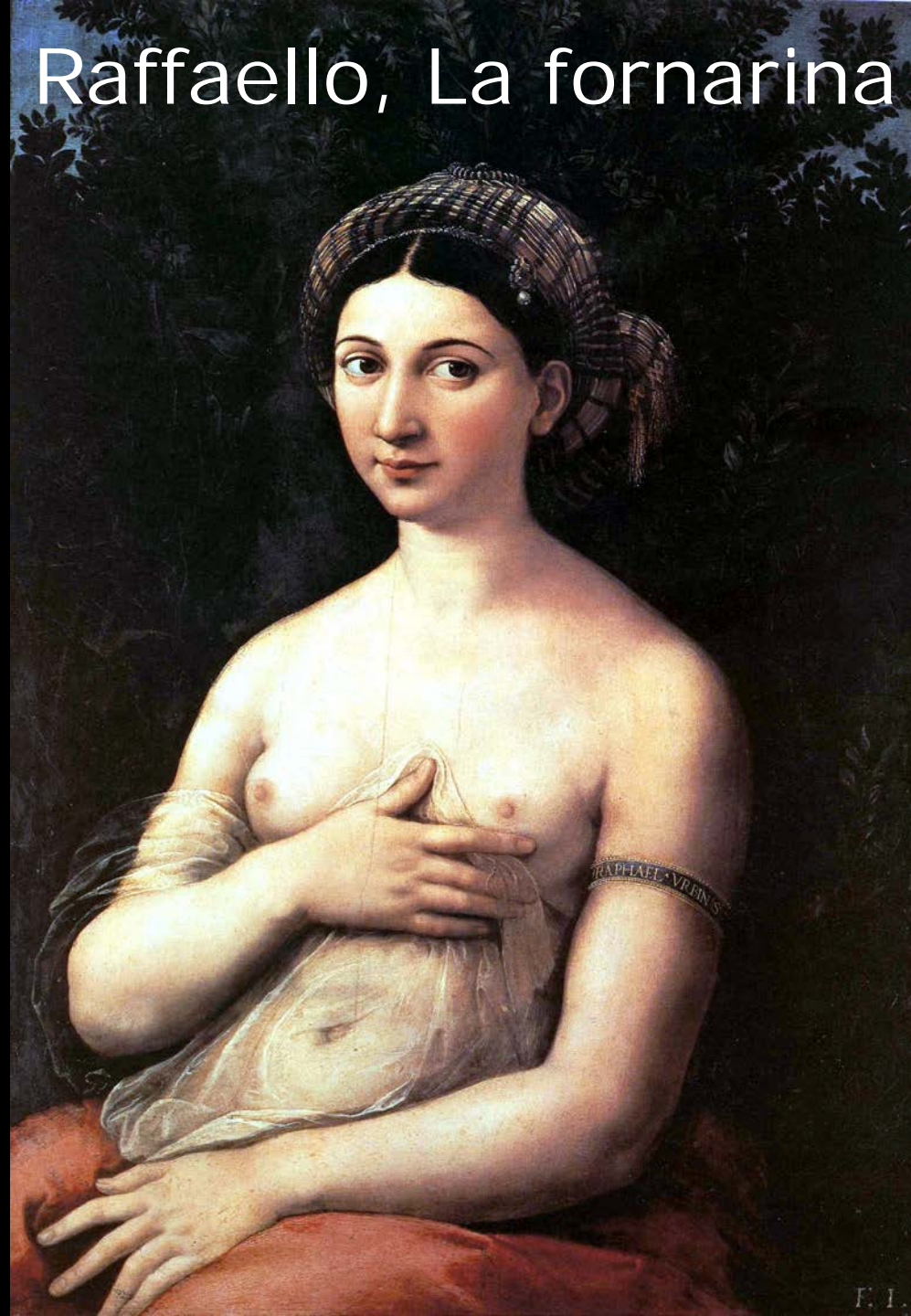
# Storia del cancro mammario



Teodora,  
imperatrice  
c. 540 d.C.

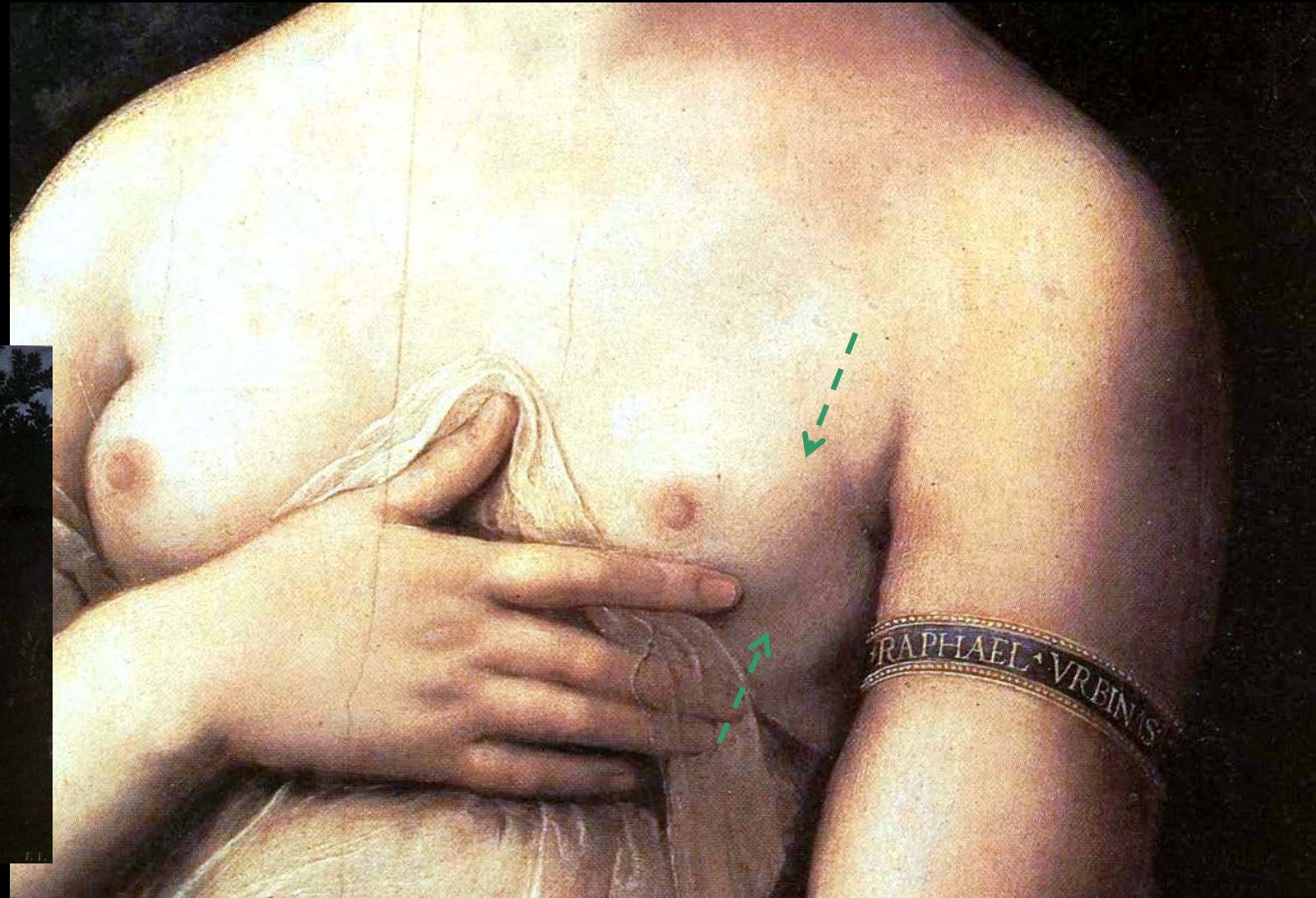


# Raffaello, La fornarina





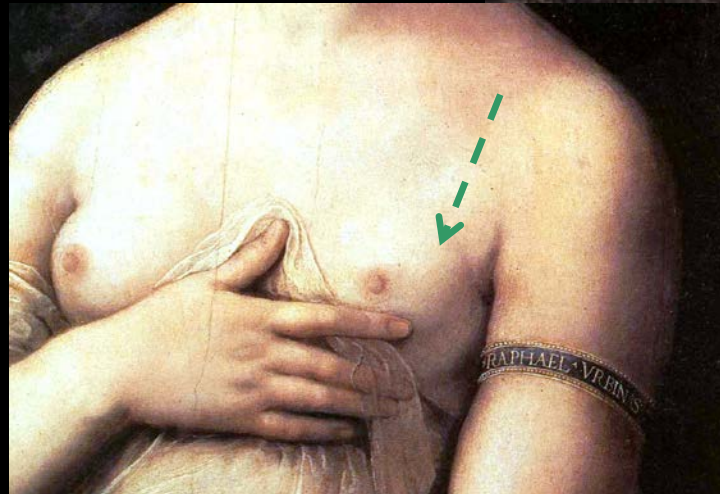
# Storia del cancro mammario





# Storia del cancro mammario

/ Raffaello / Rembrandt



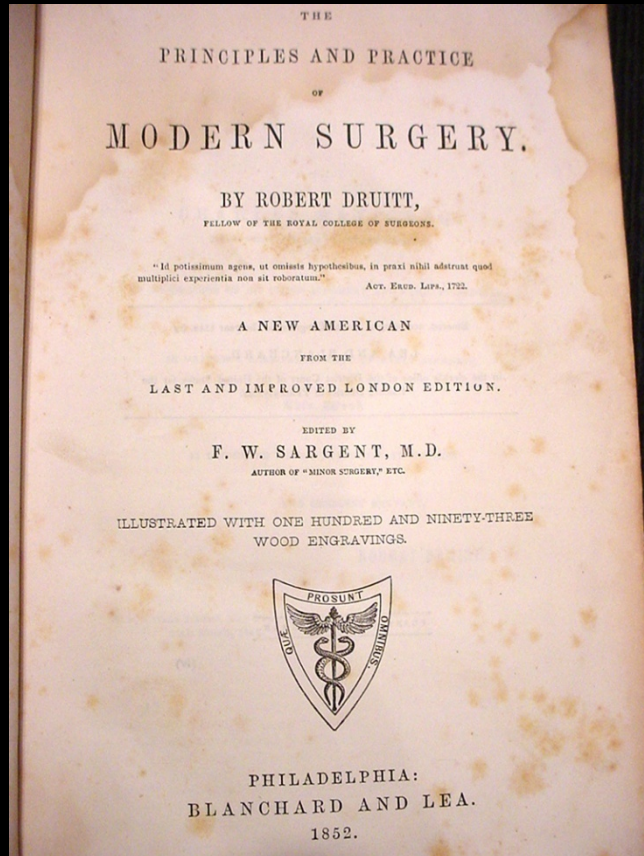
# Storia del cancro mammario / I Santi Patroni





# Storia del cancro mammario

## Chirurgia moderna, 1852



*[per il carcinoma mammario ...]*

“Possiamo solo reiterare l’opinione . . .  
che qualunque misura di ogni tipo  
sia di fatto **senza speranza** . . .”

**The Principles and Practice of Modern Surgery,**  
di Robert Druitt, FW Sargent, ed.,  
Philadelphia, Blanchard and Lea, 1852



## Storia del cancro mammario 1993

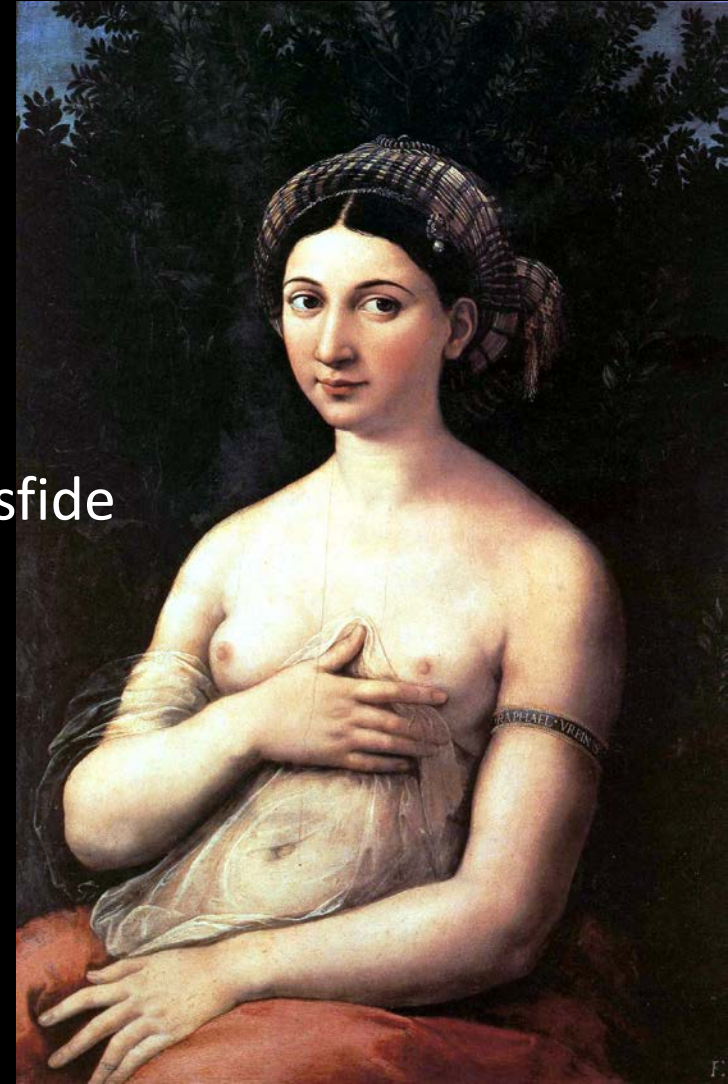
*La mano*, 1992.

Fotografia di Matuschka  
apparsa sulla copertina di *Life*  
(ottobre 1993)



# Storia dello screening mammografico / temi

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- Le polemiche sullo screening
- La nuova era dello screening: successi e sfide





## Le prove di efficacia dello screening

Sono stati condotti **studi controllati randomizzati** per dimostrare la teoria che **la diagnosi precoce realizza un impatto favorevole sulla mortalità** da cancro mammario



# Le prove di efficacia dello screening

/ gli studi clinici randomizzati prospettici

/ due studi di importanza storica

- HIP-study

(Health Insurance Plan of Greater New York)

- Swedish Two County Study





# Le prove di efficacia dello screening / lo Studio H.I.P. di New York 1963-1971

Prima pubblicazione, metodologica  
Shapiro, Strax, Venet, JAMA, 1966

## Article

February 28, 1966

### Evaluation of Periodic Breast Cancer Screening With Mammography Methodology and Early Observations

Sam Shapiro; Philip Strax, MD; Louis Venet, MD

> Author Affiliations

JAMA. 1966;195(9):731-738. doi:10.1001/jama.1966.03100090065016

## Abstract

Periodic breast cancer screening with mammography and clinical examination is being evaluated to determine its value in reducing breast cancer mortality among women. Representative samples of women aged 40 to 64 years enrolled in the Health Insurance Plan of Greater New York are randomly assigned to study and control groups, each of which will contain 30,000 women. Results of the study to date are consistent with the hypothesis that the screening leads to earlier detection of breast cancers than is ordinarily experienced and that mammography contributes significantly to detection. While these relationships are encouraging, they must be viewed with caution since the study is still in its early stages. Furthermore, the crucial question is whether mortality from breast cancer is lowered because of the screening, and definitive findings on this issue will require at least five years of follow-up.



Esame clinico di base, poi 2 gruppi randomizzati:

\* esame clinico *associato con* mammografia

\* gruppo di controllo



# Le prove di efficacia dello screening / **Io Studio H.I.P. di New York 1963-1971**

Seconda pubblicazione, primi risultati  
Shapiro, Strax, Venet, JAMA, 1971

## Article

March 15, 1971

## Periodic Breast Cancer Screening in Reducing Mortality From Breast Cancer

Sam Shapiro; Philip Strax, MD; Louis Venet, MD

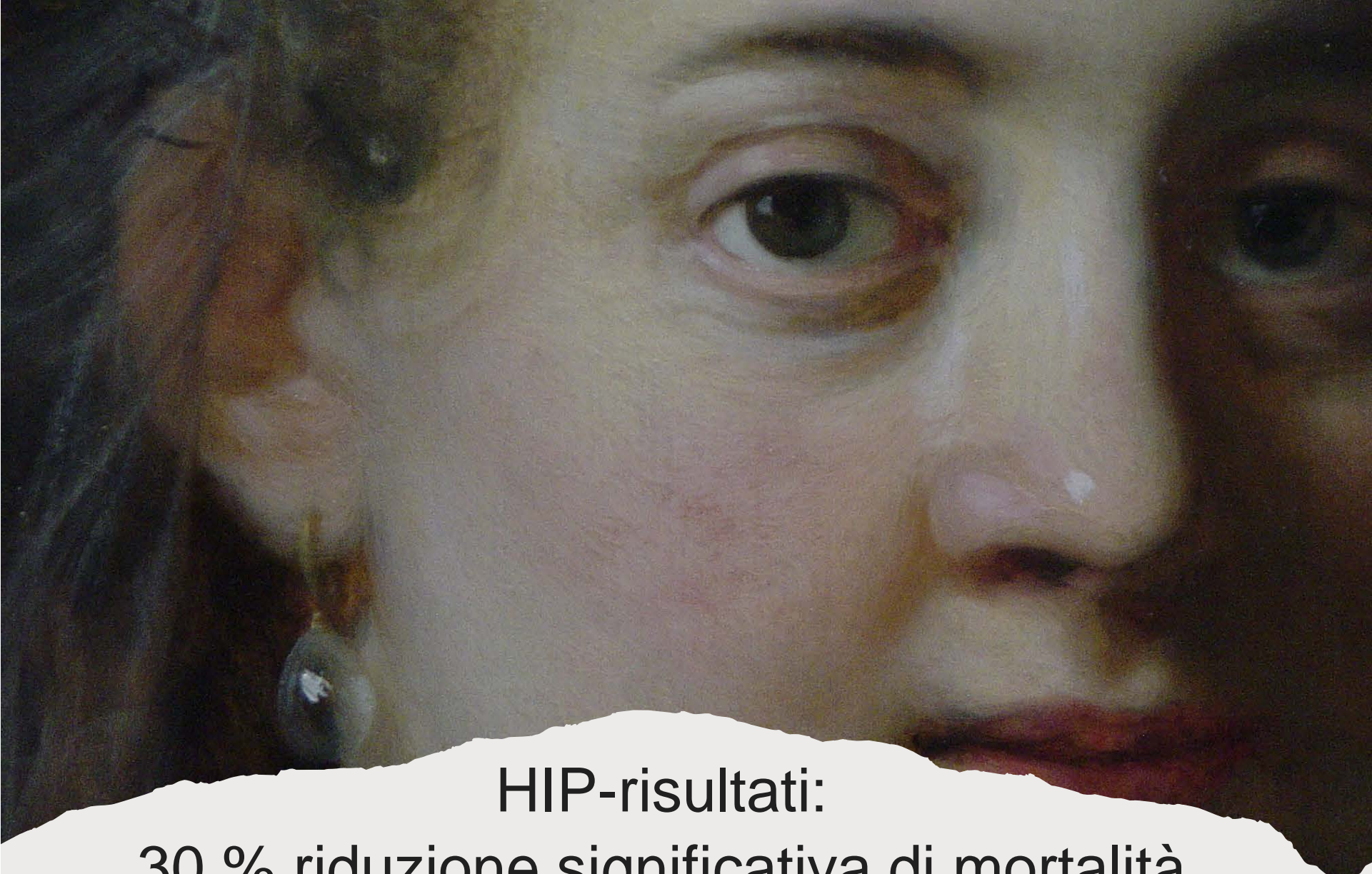
» [Author Affiliations](#)

*JAMA*. 1971;215(11):1777-1785. doi:10.1001/jama.1971.03180240027005

## Abstract

First results in a long-term investigation to determine whether periodic breast cancer screening with mammography and clinical examination leads to lowered breast cancer mortality provide grounds for cautious optimism. The study compares the experience in a random sample of 31,000 women, aged 40 to 64 years, offered screening examinations with the experience in a similarly constituted "control" group. There were 52 deaths due to breast cancer in the control group, as compared with 31 breast cancer deaths in the study group, in the period available for follow-up. The 3 1/2-year case fatality rates among women with histologically confirmed breast cancers reinforce the impression that screening leads to lowered mortality. More time, possibly ten years of follow-up, is needed to establish whether the effect of the screening program is short-term or long-term.



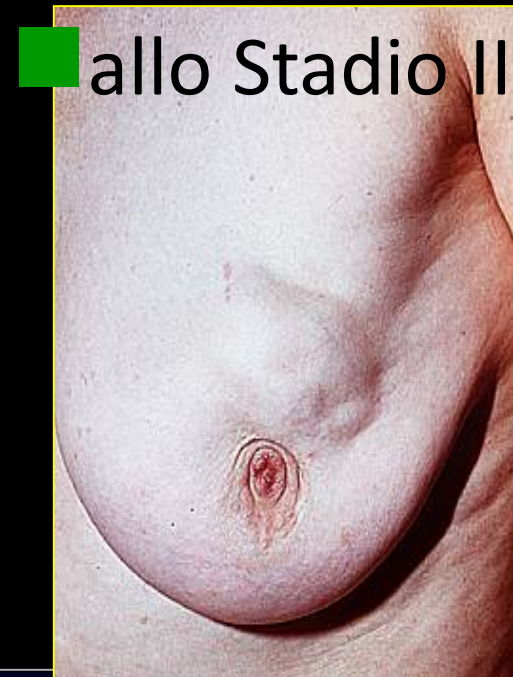


HIP-risultati:

30 % riduzione significativa di mortalità  
da cancro mammario

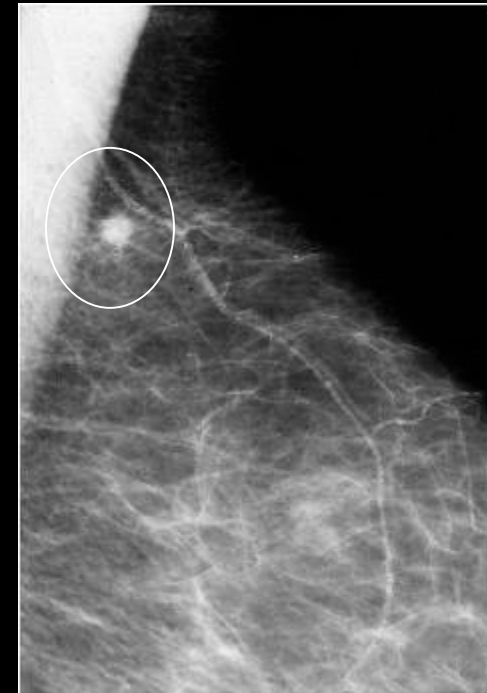


# HIP-risultati: 30 % riduzione significativa di mortalità da cancro mammario



■ **HIP-study:** Slittamento di Stadio tra le categorie di Stadio avanzato (da Stadio III-IV a Stadio II).

■ A metà degli anni 70' divenne disponibile una nuova tecnologia avanzata: l'invenzione della mammografia schermo-film a basse dosi di radiazioni, che rese possibile scoprire i tumori nella loro fase non-palpabile

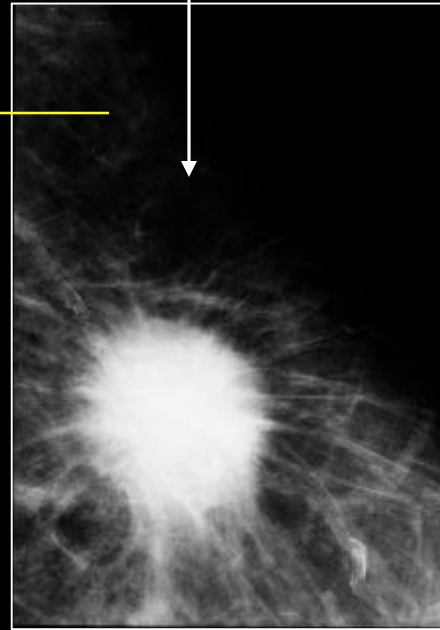




# *Lo Studio delle Due Contee Svedesi*



Due Contee



HIP-era

Stadio II



Stadio III-IV

*C'era bisogno di confermare la possibilità di scoprire il cancro con la sola mammografia*

# Studio delle Due Contee Svedesi (1976-1985)

Primi risultati pubblicati 1985

Tabar L et al, Lancet, 325, 829-832, 1985

THE LANCET



Volume 325, Issue 8433, 13 April 1985, Pages 829-832

## REDUCTION IN MORTALITY FROM BREAST CANCER AFTER MASS SCREENING WITH MAMMOGRAPHY: Randomised Trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare

L Tabár, A Gad, L.H Holmberg, U Ljungquist, [Kopparberg County Project Group](#)<sup>a</sup>,  
C.J.G Fagerberg, L Baldetorp, O Grönroft, B Lundström, J.C Månson,  
[Östergötland County Project Group](#)<sup>b</sup>, G Eklund, N.E Day, F Pettersson

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[https://doi.org/10.1016/S0140-6736\(85\)92204-4](https://doi.org/10.1016/S0140-6736(85)92204-4)

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### Abstract

A randomised controlled trial to investigate the efficacy of mass screening with singleview mammography in reducing mortality from breast cancer was started in Sweden in 1977. 162 981 women aged 40 years or more and living in the counties of Kopparberg and Östergötland were enrolled in the study and divided at random into 2 groups. Each woman in the study group was offered screening every 2 or 3 years depending on age. Women in the control group were not offered screening. This report is confined to the 134 867 women aged 40-74 years at date of entry. The results to the end of 1984 show a 31% reduction in mortality from breast cancer and a 25% reduction in the rate of stage II or more advanced breast cancers in the group invited to screening. 7 years after the start of the study the excess of stage I cancers in the study group largely outweighs the deficit of advanced cancers.





## Studio delle Due Contee Svedesi (1976-1985)

Vari aggiornamenti pubblicati

Tabar L et al, Radiology, 260 (3), 658-63, 2011

**Swedish Two-County Trial:** Impact  
of Mammographic Screening on  
Breast Cancer Mortality during  
3 Decades<sup>1</sup>

Radiology

Randomized Controlled Trial > Radiology. 2011 Sep;260(3):658-63.

doi: 10.1148/radiol.11110469. Epub 2011 Jun 28.

### Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades

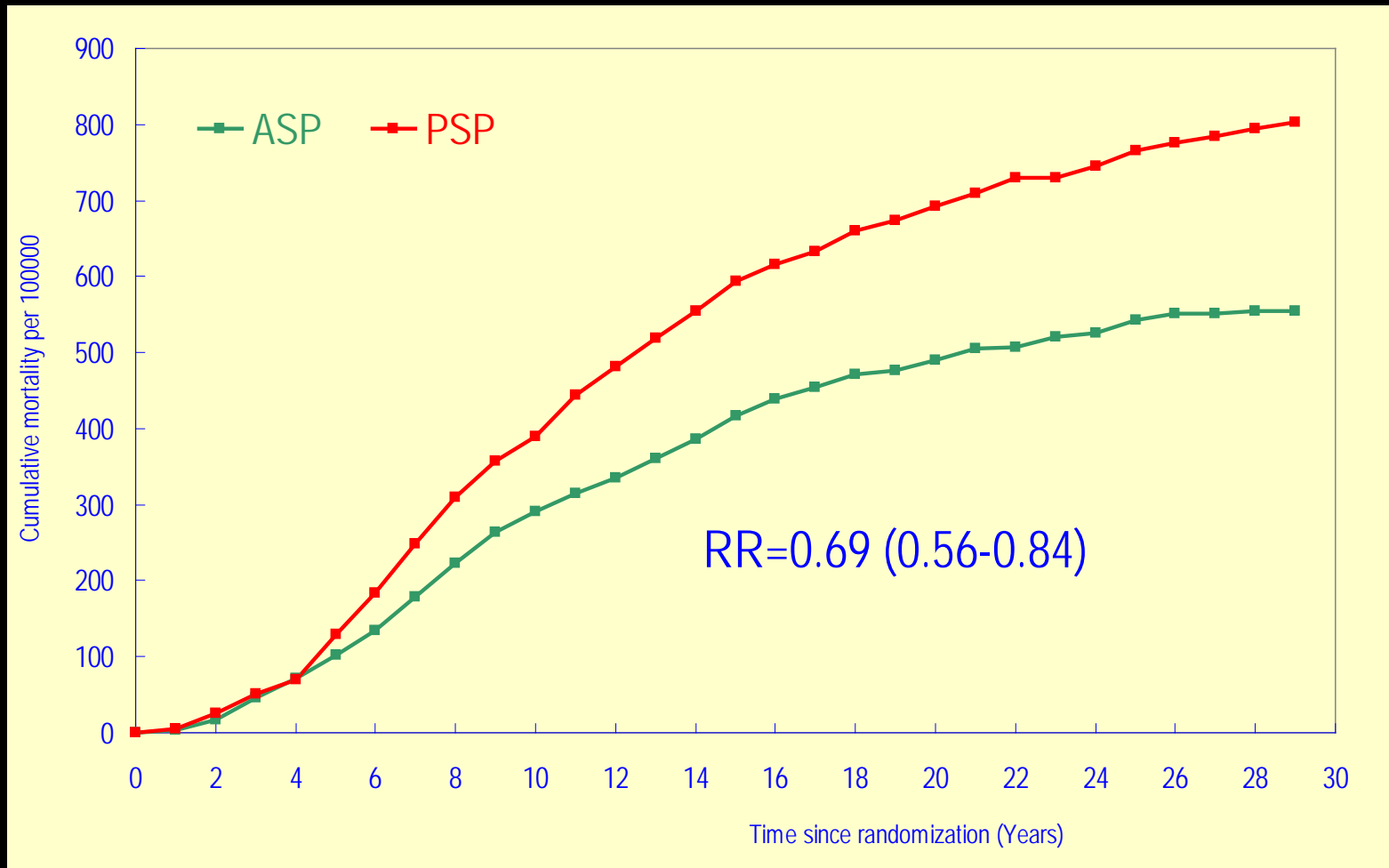
László Tabár <sup>1</sup>, Bedrich Vitak, Tony Hsiu-Hsi Chen, Amy Ming-Fang Yen, Anders Cohen, Tibor Tot, Sherry Yueh-Hsia Chiu, Sam Li-Sheng Chen, Jean Ching-Yuan Fann, Johan Rosell, Helena Fohlin, Robert A Smith, Stephen W Duffy

Affiliations + expand

PMID: 21712474 DOI: 10.1148/radiol.11110469

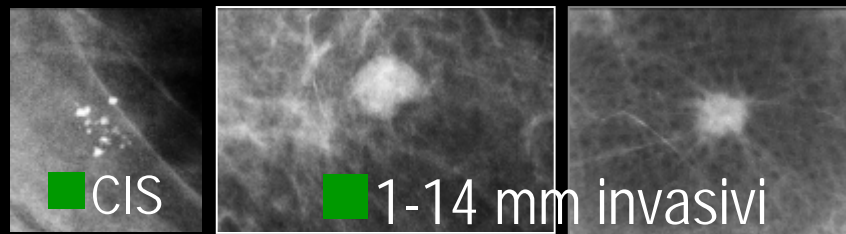
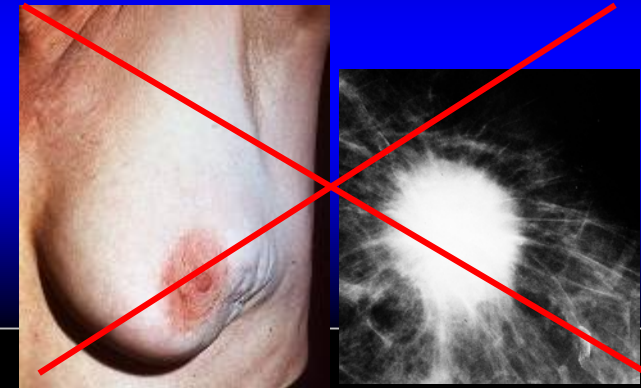
# Risultati

Significativa riduzione di mortalità





*La diagnosi precoce e la terapia possono fermare la progressione della malattia*



Diagnosi clinica

Diagnosi

mammografica

**Riducendo il tasso di cancro avanzati**

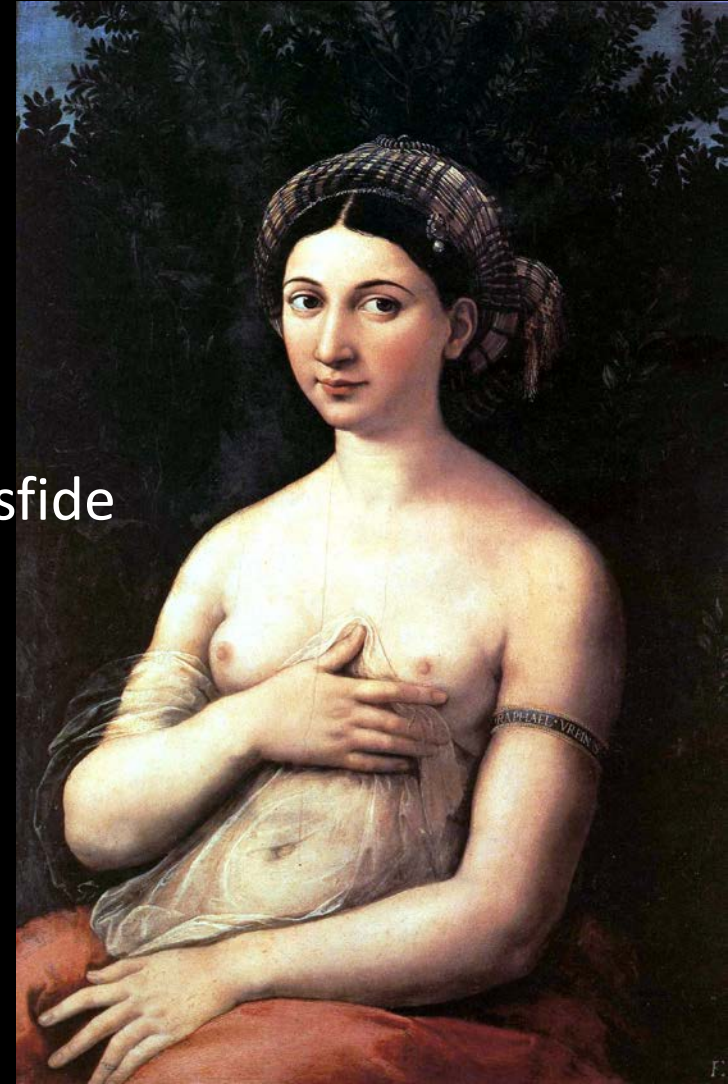
**Si riducono le morti da carcinoma mammario**

■ Shapiro S, SraxP, Venet L et al. JAMA 1971 March 15

■ Tabar L, Fagerberg G et al. Lancet 1985; 1:829-832

# Storia dello screening mammografico / temi

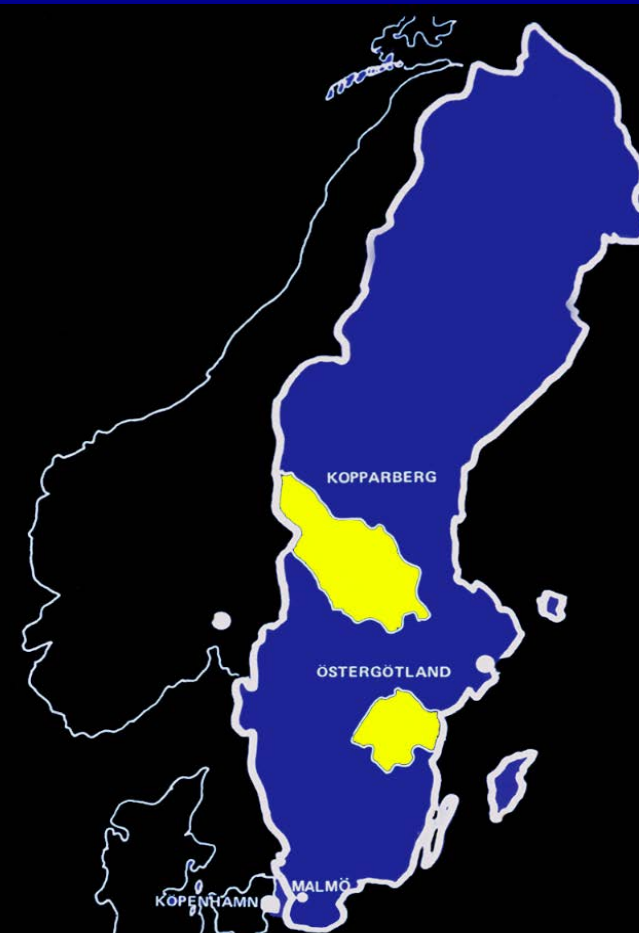
- Storia del cancro mammario
- Le prove di efficacia dello screening
- La diffusione dello screening
- Le polemiche sullo screening
- La nuova era dello screening: successi e sfide





# Diffusione dello screening

Lo Studio Svedese delle Due Contee ha fornito i fondamenti scientifici per la diffusione dello screening mammografico di popolazione in tutto il mondo



# *L'impatto degli Studi Svedesi*

*Parecchie nazioni hanno deciso di incominciare un programma di screening mammografico nazionale sulla scia dello Studio delle Due Contee*

■ Finlandia



■ Regno Unito



■ Olanda





# *L'impatto degli Studi Svedesi*

*Parecchie nazioni hanno deciso di incominciare un programma di screening mammografico nazionale sulla scia dello Studio delle Due Contee*

■ Islanda



■ Canada



■ Australia



# Diffusione dello screening / Italia / 1

Lo **Studio HIP (1963-1971)** ha portato alla nascita in Italia nel corso degli **anni '70** di alcune piccole esperienze locali di screening a Brescia e dintorni, in Piemonte (Savigliano) e – più rilevante – nella cintura di Firenze con il Gruppo del CSPO (Maltoni, Rosselli Del Turco, Ciatto)

Lo **Studio delle Due Contee (1985)** e altri studi hanno poi spinto alla **fine degli anni '80** alla progettazione di più strutturati programmi di popolazione, i primi dei quali furono nella Città di **Firenze (1990)** e nella Città di **Torino (1991-92)**



## Diffusione dello screening / Italia / 2

Il GISMa, creato dapprima come Gruppo di Studio della Scuola Italiana di Senologia (Venezia 1990) e poi costituitasi come Società Scientifica Autonoma (Vinci, Firenze, 2003) ha contribuito molto allo sviluppo dei programmi di screening italiani, in collaborazione con gli organi regionali e con l'ONS (Osservatorio Nazionale Screening) istituito nel 2001, con la partecipazione del GISMa.

## Diffusione dello screening / Italia / 3

Si deve ricordare, oltre agli importanti aspetti di tipo logistico, le difficoltà negli anni '90 incontrate nella progettazione dei programmi di screening di popolazione, anche per situazioni di **ostilità latente o dichiarata di alcune fasce del mondo clinico** e in particolare di ampi settori della Società Italiana di Radiologia (SIRM).

Tali situazioni di conflittualità si sono gradualmente risolte a partire dai primi anni 2000 con un grande lavoro di confronto e collaborazione tra i rappresentanti delle due società scientifiche.



# Diffusione dello screening / Italia / 4

Lo stato attuale della diffusione dello screening in Italia sarà come sempre oggetto di questo Convegno Annuale della Società.

# Storia dello screening mammografico

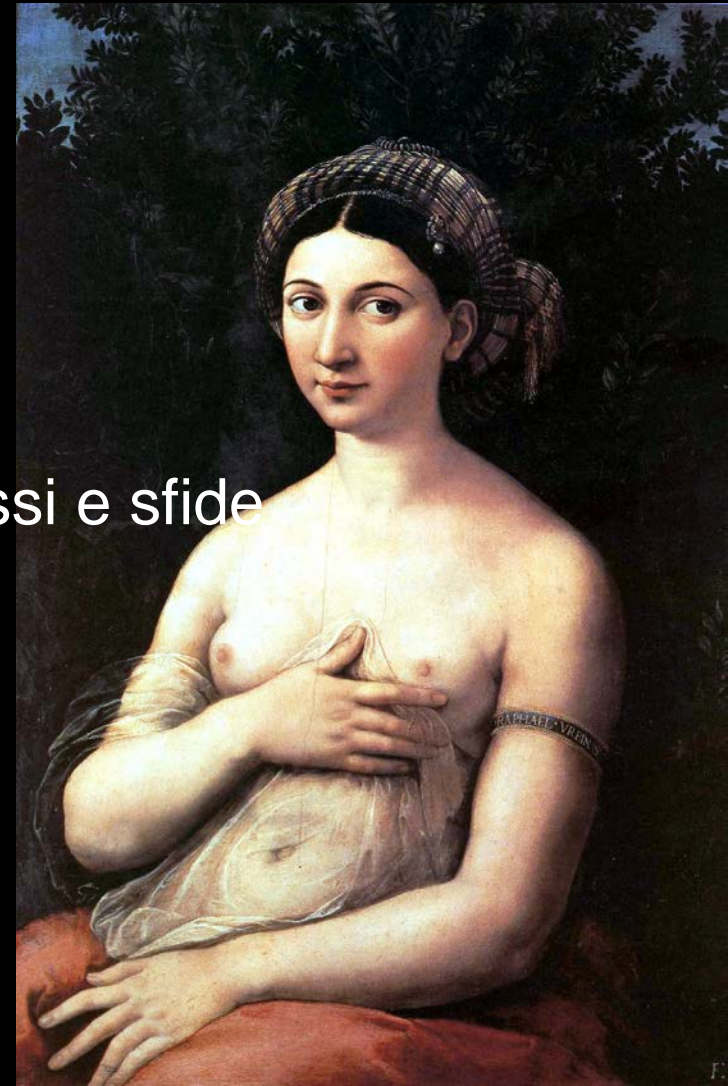
Storia del cancro mammario

Le prove di efficacia dello screening

La diffusione dello screening

**Le polemiche sullo screening**

La nuova era dello screening: successi e sfide





# Le polemiche sullo screening

Numerose, continue, incessanti

Infondate, contrarie ai dati e alle prove scientifiche

# Screening for breast cancer with mammography

Peter C Gøtzsche <sup>1</sup>, Margrethe Nielsen

Affiliations  expand

PMID: 21249649 DOI: [10.1002/14651858.CD001877.pub4](https://doi.org/10.1002/14651858.CD001877.pub4)



**Main results:** Eight eligible trials were identified. We excluded a biased trial and included 600,000 women in the analyses. Three trials with adequate randomisation did not show a significant reduction in breast cancer mortality at 13 years (relative risk (RR) 0.90, 95% confidence interval (CI) 0.79 to 1.02); four trials with suboptimal randomisation showed a significant reduction in breast cancer mortality with an RR of 0.75 (95% CI 0.67 to 0.83). The RR for all seven trials combined was 0.81 (95% CI 0.74 to 0.87). We found that breast cancer mortality was an unreliable outcome that was biased in favour of screening, mainly because of differential misclassification of cause of death. The trials with adequate randomisation did not find an effect of screening on cancer mortality, including breast cancer, after 10 years (RR 1.02, 95% CI 0.95 to 1.10) or on all-cause mortality after 13 years (RR 0.99, 95% CI 0.95 to 1.03). Numbers of lumpectomies and mastectomies were significantly larger in the screened groups (RR 1.31, 95% CI 1.22 to 1.42) for the two adequately randomised trials that measured this outcome; the use of radiotherapy was similarly increased.

# Screening for breast cancer with mammography

Peter C Gøtzsche <sup>1</sup>, Margrethe Nielsen

Affiliations + expand

PMID: 21249649 DOI: [10.1002/14651858.CD001877.pub4](https://doi.org/10.1002/14651858.CD001877.pub4)



**Authors' conclusions:** Screening is likely to reduce breast cancer mortality. As the effect was lowest in the adequately randomised trials, a reasonable estimate is a 15% reduction corresponding to an absolute risk reduction of 0.05%. Screening led to 30% overdiagnosis and overtreatment, or an absolute risk increase of 0.5%. This means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged and 10 healthy women, who would not have been diagnosed if there had not been screening, will be treated unnecessarily. Furthermore, more than 200 women will experience important psychological distress for many months because of false positive findings. It is thus not clear whether screening does more good than harm. To help ensure that the women are fully informed of both benefits and harms before they decide whether or not to attend screening, we have written an evidence-based leaflet for lay people that is available in several



# Le polemiche sullo screening

## La lettera a Lancet, 2011

Correspondence

### Effect of population-based screening on breast cancer mortality

#### Effect of population-based screening on breast cancer mortality

Although the wider scientific community has long embraced the benefits of population-based breast screening, there seems to be an active anti-screening campaign orchestrated in part by members of the Nordic Cochrane Centre. These contrary views are based on erroneous interpretation of data from cancer registries and peer-reviewed articles. Their specific aim seems to be to support a pre-existing opposition to all forms of screening.<sup>1</sup>

These individuals, making claims of poor methods, selectively discount overwhelming scientific evidence from numerous randomised trials in different countries that organised screening reduces breast cancer mortality. They claim that the significant decrease in breast cancer mortality achieved by screening is due to improvements in treatment alone, discounting the benefits of early detection. If true, this would imply that breast cancer is an exception among adenocarcinomas in that early detection does not improve prognosis—a claim contrary to the evidence.

For women with breast cancer, early detection also results in improved quality of life from less extensive surgical treatment. Women with screen-detected breast cancer in the UK have half the mastectomy rate of women with symptomatic cancers—ie, 27% versus 53%.<sup>2</sup>

Organised, high-quality breast screening is an important public health initiative by numerous governments worldwide. These policies are based on robust and extensive analysis of individualised patient data from scientific trials, with particular attention paid to the balance of potential benefits and harms.<sup>3</sup> To imply that such an international action is mass misrepresentation, or that screening is done for the benefit

of self-interested professionals, is as perverse as it is unjustified.

Comprehensive guidelines deal with the entire screening process.<sup>4</sup> Organisations responsible for screening programmes regularly review published evidence on the effects of mammographic screening, and also contradictory interpretations.

We consider the interpretation by Jørgensen, Keen, and Getzsche,<sup>5</sup> of the balance of benefits and harms to be scientifically unsound. Women would be better served by focusing efforts on how best, and not whether, to provide breast screening.

The signatories below, charged with provision and implementation of breast screening in many different countries, remain convinced that the scientific foundation for population-based, quality-assured, organised breast screening is one of the major accomplishments of the translation of clinical cancer research into public health practice. Early detection, in combination with appropriate treatment, significantly lowers breast cancer mortality and improves the life quality of patients with the disease.

We declare that we have no conflicts of interest.

Karin Bock, Bettina Borisch,  
Jenny Cawson, Berit Damtjernhaug,  
Chris de Wolf, Peter Dean,  
Ard den Heeten, Gregory Doyle,  
Rosemary Fox, Alfonso Frigario,  
Fiona Gilbert, Gerold Hecht,  
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Patricia Nisbet, Ann O'Doherty,  
Julietta Patnick, Nick Perry,  
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Vitor Rodrigues,  
Marco Rosselli Dal Turco,  
Astrid Scharpantgen, Walter Schwartz,  
Brigitte Seradour, Per Skaane,  
Laszlo Tabar, Sven Tornberg, Giske Ursin,  
Erik Van Limbergen,  
Anne Vandenbroucke, Linda J Warren,  
Lee Warwick, Martin Yaffe, Marco Zappa  
julietta.patnick@cancerscreening.nhs.uk

National Reference Center South-West, Marburg, Germany (KB); Europa Donna: the European Breast Cancer Coalition, Milan, Italy (BB); St Vincent's BreastScreen, Fitzroy VIC, Australia (JF); Norwegian Breast Cancer Screening Programme, Oslo, Norway (BD); Swiss Breast Cancer Screening Federation, Bern, Switzerland (GWW); Turku University Hospital, Turku, Finland (PD); Expertise and Training Center for Breast Cancer Screening, Nijmegen, Netherlands (AaB); National Committee—Canadian Breast Cancer Screening Initiative, Ottawa, ON, Canada (GD); Screening Division, Public Health Wales, Cardiff, UK (RF); Reference Centre for Quality Assurance, Regional Breast Cancer Screening Programme, Piemonte, Italy (AF); University of Aberdeen, UK (FG); National Reference Center North, Oldenburg, Germany (GH); National Reference Center Münster, Münster, Germany (WH); National Reference Center Munich, Munich, Germany (SH-K); EUREF Certification Programme of the German Population-Based Breast Screening Programme, Nijmegen, Netherlands (RH); Sydney Breast Clinic, Sydney, NSW, Australia (FJ); Breast Screening, Central Denmark Region, Århus, Denmark (AL); MAMMa Healthcare Institute, Budapest, Hungary (SM); Northern Ireland Breast Screening Programme, Belfast, UK (AM); Cancer Screening Services, Queensland Health, Brisbane, QLD, Australia (MJ); Jersey Breast Screening Service, St Helier, UK (PN); Breast Screening, Dublin, Ireland (AO'D); NHS Cancer Screening Programmes, Sheffield S10 3TH, UK (JP); European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis, London, UK (NP); National Reference Center Berlin, Berlin, Germany (G-R-J); Faculty of Health Sciences, Sydney University, Sydney, NSW, Australia (MR); Portuguese Central Region Breast Cancer Screening Programme, Coimbra, Portugal (VR); EUREF, Florence, Italy (MMDT); Programmes Prevention Cancer, Luxembourg (AS); Mammography Centre, Odense Universitetshospital, Odense, Denmark (WS); Programme National de Dépistage Mammellaire, France (RS); Mammography Screening, Oslo, Norway (PS); Department of Mammography, Falun Central Hospital, Falun, Sweden (T); Stockholm Götaland Regional Cancer Screening Programmes, Stockholm, Sweden (ST); Cancer Registry of Norway, Oslo, Norway (GU); LUCK, Louvain University Centre for Cancer Prevention, Louvain, Belgium (EV-L); Cancer Screening, Wallonia, Belgium (AV); Screening Mammography Program of British Columbia, University of British Columbia, Vancouver, BC, Canada (JW); BreastScreen NSW, Eveleigh, NSW, Australia (LW); Imaging Research Program, Ontario Institute for Cancer Research, Toronto, ON, Canada (MY); and Italian National Centre for Screening Monitoring, Florence, Italy (MZ)



See Editorial page 1758

Although the wider scientific community has long embraced the benefits of population-based breast screening, there seems to be an active anti-screening campaign orchestrated in part by members of the Nordic Cochrane Centre. These contrary views are based on erroneous interpretation of data from cancer registries and peer-reviewed articles. Their specific aim seems to be to support a pre-existing opposition to all forms of screening.<sup>1</sup>

These individuals, making claims of poor methods, selectively discount overwhelming scientific evidence from numerous randomised trials in different countries that organised screening reduces breast cancer mortality. They claim that the significant decrease in breast cancer mortality achieved by screening is due to improvements in treatment alone, discounting the benefits of early detection. If true, this would imply that breast cancer is an exception among adenocarcinomas in that early detection does not improve prognosis—a claim contrary to the evidence.

1 Getzsche P. Screening for colorectal cancer. *Lancet* 1997; **349**: 356.  
2 Lawrence G, Keenan D, Lagard C, et al. Second all breast cancer report, June 2011. <http://www.ncin.org.uk/view.aspx?rid=612> (accessed Nov 4, 2011).  
3 International Agency for Research on Cancer. Breast cancer screening. IARC handbook of cancer prevention volume 7. Lyon: IARC press, 2002. <http://www.iarc.fr/en/publications/pdfs-online/prevention/handbook7/index.php> (accessed Nov 4, 2011).

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# Le polemiche sullo screening: analisi e risposte

## Radiological Screening of Breast Cancer: Evolution

17

Alfonso Frigerio, Francesco Sardanelli, and Franca Podo

### Radiological Screening of Breast Cancer: Evolution

17

Alfonso Frigerio, Francesco Sardanelli, and Franca Podo

#### Abbreviations

AWBU	Automated whole-breast ultrasound
BC	Breast cancer
CAD	Computer-aided diagnosis
CC	Case-control
CE	MRI Contrast-enhanced magnetic resonance imaging
CI	Confidence interval
CNIBSS	Canadian National Breast Screening Study
CRT	Chest radiation therapy
DBT	Digital breast tomosynthesis
HIP	Health Insurance Plan
HR	High risk
IBM	Incidence-based mortality
IT	Information technology
LIR	Lifetime risk
MR	Magnetic resonance
MS	Mammography screening
NBCSP	Norwegian Breast Cancer Screening Programme
NCR	Nordic Cochrane review
NNS	Number needed to screen

OR	Odds ratio
PPV	Positive predictive value
RCT	Randomized controlled trial
RR	Relative risk
STC	Swedish Two County
TNBC	Triple negative breast cancer
US	Ultrasound
USPSTF	US Preventive Services Task Force

#### 17.1 Normal Risk Population

Alfonso Frigerio

**Abstract** Mammography screening is one of the revolutionary advances in the fight against breast cancer, alongside breast-conserving surgery. Few medical interventions have been so extensively evidence-based and yet subjected to persistent critiques. The clear scientific evidence of the efficacy of screening in reducing breast cancer mortality is discussed. Benefits provided by screening are substantial, well above any negative effect. In the age of modern treatment, early detection still contributes to breast cancer mortality reduction.

A full appreciation is advocated for organized screening programs and the added value they provide in terms of high quality, equitable health service, and as the optimal environment where best capitalize on the new advances in treatment. Future evolution might include (a) tailored, risk-based protocols, in the first place extending the age range of offered screening; (b) new imaging tools; and (c) optimization of existing programs, through better monitoring, training, and research—always abiding by the big caveats: evidence of efficacy, incremental cost-effectiveness, and sustainability.

Both screening and treatment have merits in achieving mortality reduction. It would be clever to recognize their mutual enhancing power and devote resources to a very appropriate topic for research: how early detection might or should change the treatment of breast cancer.

A. Frigerio (✉)  
Regional Reference Center for Breast Cancer Screening,  
City of Health and Science Hospital, Turin, Italy  
e-mail: [alfredofrigerio@unito.it](mailto:alfredofrigerio@unito.it)

F. Sardanelli (✉)  
Department of Biomedical Sciences for Health, University of  
Milan, Unit of Radiology, Research Hospital (IRCCS)  
Policlinico San Donato, Via Medardi, 30, 20097  
San Donato Milanese, Milan, Italy  
e-mail: [francesco.sardanelli@unimi.it](mailto:francesco.sardanelli@unimi.it)

F. Podo  
Department of Cell Biology and Neurosciences,  
Istituto Superiore di Sanità, Viale Regina Elena 299,  
00161 Rome, Italy  
e-mail: [franca.podo@ispc.it](mailto:franca.podo@ispc.it)

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# Le polemiche sullo screening: una sequenza provocatoria

It is still unfortunate that what has been opportunely defined as “an active anti-screening campaign [...] based on erroneous interpretation of data from cancer registries and peer-reviewed articles” [6] has been kept alive over the last two decades to this day, with a disconcerting pattern of following waves. This process may be described as a “provocative sequence” of:

- (a1) Main question
- (a2) Scientific proof provided
- (a3) Evidence questioned on poor or unsubstantiated terms
- (a4) Evidence (to some extent) conceded, but then
- (b1) New question set forward
- (b2) Scientific proof provided - etc, through (d4)



# Le polemiche sullo screening: una sequenza provocatoria / Nordic Cochrane Centre

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- (a) Can MS reduce BC mortality?—**the efficacy issue:** (a1) evidence provided by the big RCTs; (a2) evidence questioned, most pugnaciously by the Nordic Cochrane Centre; (a3) evidence eventually (to some extent) conceded in subsequent articles; and (a4) new issue set forward about effective reproducibility of trial results into public health practice.
- (b) Can MS service programs reproduce the results of the RCTs and actually save lives in a sustainable way in the context of the health-care system?—**the effectiveness issue:** (b1) evidence provided by a large number of observational studies; (b2) evidence questioned, mostly on the basis of methodologically poor “ecological” studies, lacking information about actual exposure of women to MS; (b3) evidence eventually conceded in subsequent articles; and (b4) new issue set forward about “harms” of screening surpassing the possible benefits.

benefits.

(c) Are the benefits provided by MS more substantial than any unwanted effect that it may produce?—**the harm/benefit balance** analysis of MS: (c1) evidence of a favorable balance provided by many researchers and prominently in the Euroscreen Working Group analysis; (c2) evidence questioned, especially on the basis of grossly inflated estimates of overdiagnosis; (c3) evidence conceded, most authoritatively by the UK Independent Panel [7], the “Marmot report;” (c4) new issue set forward about any remaining significance of the role of early detection in the new age of effective cancer treatment.

(d) Even after MS was proved valid and effective by RCTs and even conceding that its side effects could be minor in respect to the potential benefits, does early detection through MS still hold its meaning in the new era where very effective new treatments for BC have become available? Is it not the case that most of the BC mortality reduction that has been recently observed should be credited to treatment rather than MS?—**the “expired validity” issue** of MS: (d1) evidence has been provided confirming a substantial net benefit of screening on top of the achievements of treatment and (d2) discussion on this point (d3–d4) will be commented in the following pages.

Le polemiche sullo screening:  
una sequenza provocatoria / Nordic Cochrane Centre



## Early diagnosis, not differential treatment, explains better survival in service screening

Eugenio Paci <sup>a,\*</sup>, Antonio Ponti <sup>b</sup>, Marco Zappa <sup>a</sup>, Silvia Patriarca <sup>c</sup>, Patrizia Falini <sup>a</sup>,  
Gabriella Delmastro <sup>b</sup>, Simonetta Bianchi <sup>d</sup>, Anna Sapino <sup>e</sup>, Vania Vezzosi <sup>d</sup>,  
Carlo Senore <sup>b</sup>, Emanuele Crocetti <sup>a</sup>, Alfonso Frigerio <sup>f</sup>, Roberto Zanetti <sup>c</sup>,  
Marco Rosselli del Turco <sup>g</sup>, Nereo Segnan <sup>b</sup>

<sup>a</sup> *Unit of Clinical and Descriptive Epidemiology, Centre for Study and Prevention of Cancer, Research Institute of Tuscany Region,  
Via di San Salvi 12, 50125 Firenze, Florence, Italy*

<sup>b</sup> *Unit of Epidemiology, Centre for Prevention of Cancer, Turin, Italy*

<sup>c</sup> *Piedmont Cancer Registry, Centre for Prevention of Cancer, Turin, Italy*

<sup>d</sup> *Department of Pathology, University of Florence, Florence, Italy*

<sup>e</sup> *Department of Pathology, University of Turin, Italy*

<sup>f</sup> *First Breast Screening Unit, S. Giovanni Battista Hospital, Turin, Italy*

<sup>g</sup> *Screening Unit and Scientific Director, Centre for Study and Prevention of Cancer, Research Institute of Tuscany Region, Florence, Italy*

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Le polemiche sullo screening:  
La sovradiagnosi e il rapporto Marmot, 2012-2013

BJC

REPORT

British Journal of Cancer (2013) 108, 2205–2240 | doi: 10.1038/bjc.2013.177

## The benefits and harms of breast cancer screening: an independent review

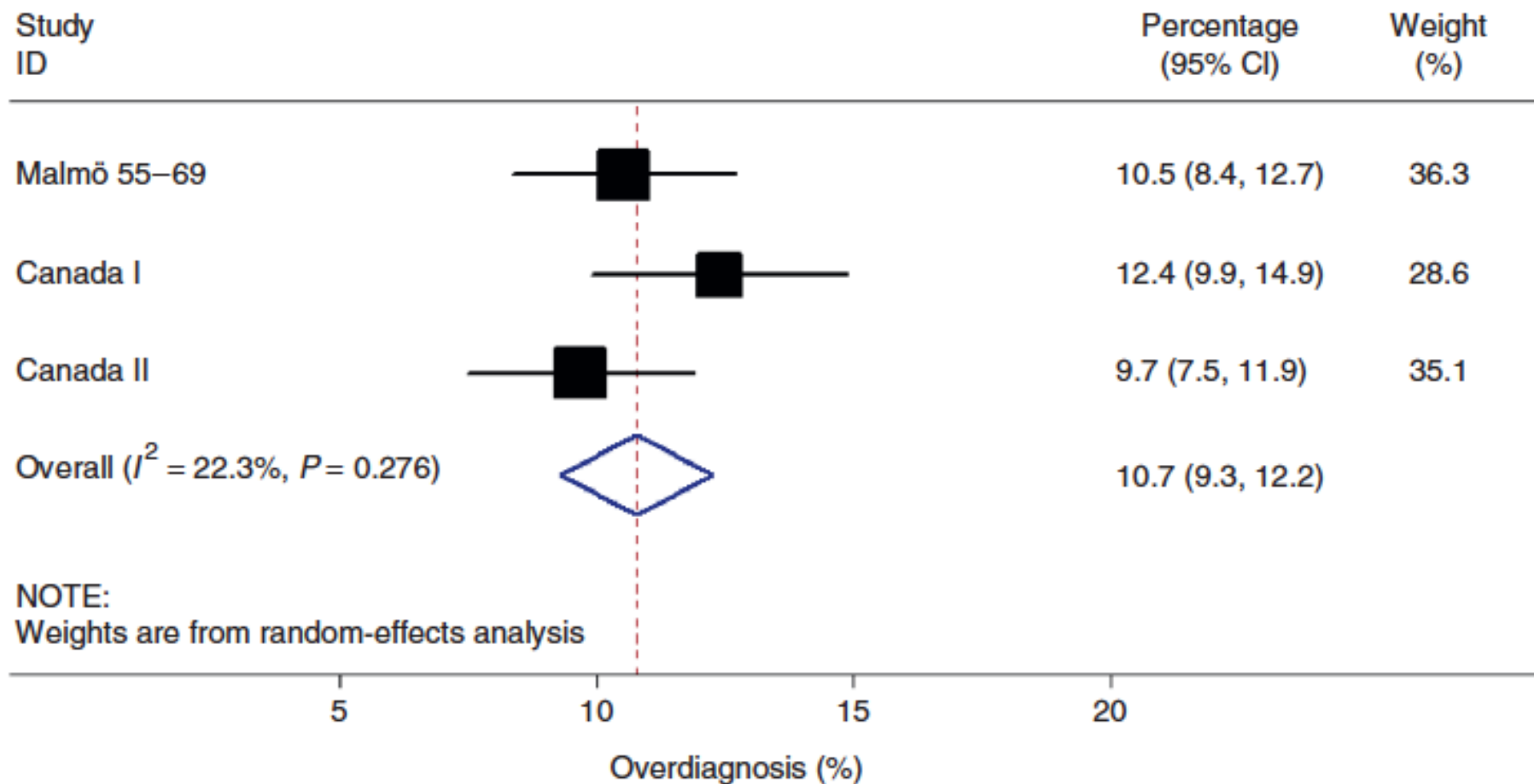
*A report jointly commissioned by Cancer Research UK and the Department of Health (England)  
October 2012.*

M G Marmot<sup>\*,1</sup>, D G Altman<sup>2</sup>, D A Cameron<sup>3</sup>, J A Dewar<sup>4</sup>, S G Thompson<sup>5</sup>, M Wilcox<sup>6</sup> – The Independent UK  
Panel on Breast Cancer Screening

# Le polemiche sullo screening: La sovradiagnosi e il rapporto Marmot, 2012-2013

## *Conclusion*

Many observational studies have been published, and their conclusions hotly contested. In general, the more contemporaneous case-control and incidence-based mortality studies support the evidence from the trials that screening does have a beneficial effect on mortality. The panel's view is that the trials provide more reliable evidence for an estimate of mortality reduction. Nevertheless, the observational studies support the hypothesis that screening continues to be beneficial in an era of improved treatment.



overdiagnosis: (a) excess cancers

proportion of cancers diagnosed over whole follow-up period in women invited for screening, |



Le polemiche sullo screening

Numerose, continue, incessanti

Infondate, contrarie ai dati e alle prove scientifiche

Il disastro canadese

# Il disastro canadese

**Table 17.1** Breast cancer mortality reduction in RCTs of mammography screening

Study, date of start	Age group	RR	95% CI	Weight (%)
New York, 1963*	40–64	0.83	0.70–1.00	16.9
Malmö I, 1976*	45–69	0.81	0.61–1.07	9.5
Kopparberg, 1977	38–75	0.58	0.45–0.76	10.7
Ostergötland, 1978	38–75	0.76	0.61–0.95	13.0
Canada I, 1980**	40–49	0.97	0.74–1.27	10.2
Canada II, 1980**	50–59	1.02	0.78–1.33	10.2
Stockholm, 1981*	39–65	0.73	0.50–1.06	6.0
Gothenburg, 1982	39–59	0.75	0.58–0.98	10.7
UK age trial, 1991*	39–49	0.83	0.66–1.04	12.8
Overall		0.80	0.73–0.89	

A meta-analysis after 13 years of follow-up, based on the Cochrane [11] and Marmot reviews [7] (modified)

*RCT* randomized controlled trial, *RR* relative risk, *CI* confidence interval


\*Studies falling short of statistical significance and/or RRs between 0.80 and 0.90

\*\*Studies with no statistical significance and RRs beyond 0.90

## RESEARCH

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# Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial

 OPEN ACCESS

Anthony B Miller *professor emeritus*<sup>1</sup>, Claus Wall *data manager*<sup>1</sup>, Cornelia J Baines *professor emerita*<sup>1</sup>, Ping Sun *statistician*<sup>2</sup>, Teresa To *senior scientist*<sup>3</sup>, Steven A Narod *professor*<sup>1 2</sup>



**Table 1| Number of breast cancers diagnosed in mammography arm and control arm, by study year**

Year of study	Mammography arm (n=44 925)		Control arm (n=44 910)	
	No of cancers detected	Mean size (cm)	No of cancers detected	Mean size (cm)
1	253	1.87	170	2.03
2	109	2.05	89	2.19
3	101	1.64	89	2.11
4	111	2.01	86	2.08
5	92	1.98	90	2.13
Subtotal years 1-5	666	1.91	524	2.10
6	83	2.15	83	2.42
7	82	1.99	93	2.24
8	107	2.01	133	2.04
9	115	1.86	119	1.90
10	127	1.69	128	1.71
Subtotal years 6-10	514	1.93	556	2.05
Subtotal years 11-25	2070	—	2053	—
Subtotal years 6-25	2584	—	2609	—
Total years 1-25	3250	—	3133	—

**Table 3| Deaths from breast cancer to 31 December 2005, by study arm and year of diagnosis. Values are numbers (percentages) unless stated otherwise**

Study year	Deaths by study arm	
	Mammography (n=44 925)	Control (n=44 910)
Deaths from breast cancers detected in years 1-5 (screening period)*:		
Screen detected, year 1	52 (28.9)	26 (15.2)
Screen detected, years 2-5	63 (35.0)	29 (17.0)
Interval cancers, years 1-5	46 (25.6)	44 (25.7)
Incident cancers, year 5	19 (10.6)	72 (42.1)
Screen period, total	180 (100)	171 (100)
Breast cancer deaths per 10 000 women from cancers detected in years 1-5	40.1	38.1
Deaths from breast cancers detected in years 6-25 (follow-up period)*		
Breast cancer deaths per 10 000 women from cancers detected in years 6-25	66.3	71.4
Total deaths(all breast cancers, all years)	500	505
Breast cancer deaths per 10 000 women (all breast cancers, all years)	108.4	110.2

\*Year of diagnosis was not available for 35 additional women, 22 in mammography arm and 13 in control arm.

# Increasingly strong reduction in breast cancer mortality due to screening

**G van Schoor<sup>\*,1</sup>, SM Moss<sup>2</sup>, JDM Otten<sup>1</sup>, R Donders<sup>1</sup>, E Paap<sup>1</sup>, GJ den Heeten<sup>3</sup>, R Holland<sup>3</sup>, MJM Broeders<sup>1,3</sup> and ALM Verbeek<sup>1,3</sup>**

RESULTS: The breast cancer death rate in the screened group over the complete period was 35% lower than in the unscreened group (OR = 0.65; 95% CI = 0.49–0.87). Analysis by calendar year showed an increasing effectiveness from a 28% reduction in breast cancer mortality in the period 1975–1991 (OR = 0.72; 95% CI = 0.47–1.09) to 65% in the period 1992–2008 (OR = 0.35; 95% CI = 0.19–0.64).

CONCLUSION: Our results show an increasingly strong reduction in breast cancer mortality over time because of mammographic screening. *British Journal of Cancer* (2011) **104**, 910–914. doi:10.1038/bjc.2011.44 www.bjcancer.com



# Dati olandesi

**Table 1** The effectiveness of mammographic screening on breast cancer mortality expressed by odds ratios, according to calendar period of index-invitation at screening and corrected for age at invitation

<b>Calendar period of index-invitation</b>	<b>Cases screened (unscreened)</b>	<b>Referents screened (unscreened)</b>	<b>Odds ratio (95% CI)</b>
1975–2008	191 (91)	1089 (321)	0.65 (0.49–0.87)
1975–1991	90 (40)	501 (149)	0.72 (0.47–1.09)
1992–2008	29 (23)	202 (58)	0.35 (0.19–0.64)

# Il disastro canadese / corretto

**Table 17.2** Breast cancer mortality reduction in RCTs of mammography screening, revised and updated

Study, date of start	Age group	RR	95% CI	Weight (%)
Malmö I, 1976*	45–69	0.81	0.61–1.07	15.2
Kopparberg, 1977	38–75	0.58	0.45–0.76	17.1
Ostergötland, 1978	38–75	0.76	0.61–0.95	20.7
Stockholm, 1981*	39–65	0.73	0.50–1.06	9.6
Gothenburg, 1982	39–59	0.70	0.53–0.93	17.1
UK age trial, 1991	39–49	0.75 <sup>§</sup>	0.58–0.97	20.4

Data derived from the Cochrane and Marmot reviews [7, 11], applying a restricted selection of trials (see text) and substituting the latest updates of the UK Age trial and of the Gothenburg trial [26, 27]

*RCT* randomized controlled trial, *RR* relative risk, *CI* confidence interval

\*Studies approaching statistical significance and RRs between 0.80 and 0.90

<sup>§</sup>RR for cancers diagnosed during the recruitment period of trial (see text for discussion)

Weight was recalculated as a proportion from Table 17.1

# Service screening with mammography in Northern Sweden: effects on breast cancer mortality – an update

Håkan Jonsson, Pál Bordás, Hans Wallin, Lennarth Nyström and Per Lenner

.....

*J Med Screen* 2007; **14**:87–93

**Objectives** To study the effectiveness of service screening with mammography in Northern Sweden.

**Setting** Two counties which invited women aged 40–74 years to service screening with mammography were compared with two counties where service screening started 5–7 years later. There were 109,000 and 77,000 women in the study and control counties, respectively.

**Methods** Cohorts in the study group were defined to include only breast cancer cases diagnosed after their first invitation to screening. Two outcome measures for breast cancer mortality were used; excess mortality and underlying cause of death (UCD). Detection mode was used to estimate the efficacy of screening for those women who actually attended screening. The cohorts were followed for 11 years.

**Results** The relative rate (RR) of breast cancer death as excess mortality and UCD for women aged 40–74 years invited to screening, compared with women not yet invited, was 0.70 (95% confidence interval [CI] 0.56–0.87) and 0.74 (95% CI 0.62–0.88), respectively. The largest effect was seen in women aged 40–49 years (RR = 0.64 and RR = 0.62 for excess mortality and UCD, respectively). RR in age 40–74 years for women actually screened was 0.65 (95% CI 0.51–0.84) and 0.70 (95% CI 0.57–0.86) for excess mortality and UCD, respectively. The number of women needed to screen to save one life was 912 after 11 years of follow-up.

**Conclusions** This study confirms previous findings in the earlier follow-up and indicates a long-term reduction of breast cancer mortality by 26–30%. The efficacy among those who actually attended screening was about 5% larger.

See end of article for authors' affiliations

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Correspondence to:  
Dr Håkan Jonsson,  
Oncological Centre, Umeå  
University Hospital, S-901  
85 Umeå, Sweden;  
hakan.jonsson@oc.umu.se

Accepted for publication  
1 February 2007

.....

impact of screening in 40-49ys old  
**RR 0.62 (0.42-0.91)**



# Effectiveness of Population-Based Service Screening With Mammography for Women Ages 40 to 49 Years

Evaluation of the Swedish Mammography Screening in Young Women (SCRY) Cohort

Barbro Numan Hellquist, MSc<sup>1</sup>; Stephen W. Duffy, MSc<sup>2</sup>; Shahin Abdsaleh, MD, PhD<sup>3</sup>; Lena Björnelid, RN<sup>4</sup>; Pál Bordás, MD<sup>5</sup>; László Tabár, MD, PhD<sup>6</sup>; Bedrich Viták, MD, PhD<sup>7</sup>; Sophia Zackrisson, MD, PhD<sup>8</sup>; Lennarth Nyström, PhD<sup>9</sup>; and Håkan Jonsson, PhD<sup>1</sup>

to 49 years. Relative risks (RRs) with 95% confidence intervals (CIs) were estimated. **RESULTS:** There was no significant difference in breast cancer mortality during the prescreening period. During the study period, there were 803 breast cancer deaths in the study group (7.3 million person-years) and 1238 breast cancer deaths in the control group (8.8 million person-years). The average follow-up was 16 years. The estimated RR for women who were invited to screening was 0.74 (95% CI, 0.66-0.83), and the RR for women who attended screening was 0.71 (95% CI, 0.62-0.80). **CONCLUSIONS:** In this comprehensive study, mammography screening for women ages 40 to 49 years was efficient for reducing breast cancer mortality. *Cancer* 2010;000:000-000. © 2010 American Cancer Society.

impact of screening in 40-49ys old  
**RR 0.74 (0.66-0.83)**

Sull'opportunità di estendere  
lo screening mammografico  
organizzato alle donne  
di 40-49 e 70-74 anni di età.  
Raccomandazioni di una  
conferenza di consenso italiana

On the opportunity of extending  
screening service  
by mammography to 40-49  
and 70-74 years of age women.  
Recommendations of a national  
Italian Consensus Conference

Vito Distante,<sup>1</sup> Stefano Ciatto,<sup>2</sup> Alfonso Frigerio,<sup>3</sup> Carlo Naldoni,<sup>4</sup> Eugenio Paci,<sup>2</sup> Antonio Ponti,<sup>5</sup> Marco Rosselli del Turco,<sup>2</sup>  
Marcello Vettorazzi,<sup>6</sup> Marco Zappa<sup>2</sup>

Epidemiol Prev. 2007 Jan-feb; 31(1): 15-22.

## **Main recommendations:**

- \* first, complete coverage of the 50-69 ys
- \* then, consider extension to other age groups
- \* if so, start from 45-49ys and 70-75ys old

## **False-positive results in the randomised controlled trial of mammographic screening from age 40 ('Age' trial)**

**Louise E Johns<sup>1,\*</sup> and Sue Moss<sup>1</sup> Age Trial Management Group**  
**Howard Cuckle<sup>2</sup>, Lynda Bobrow<sup>3</sup>, Andrew Evans<sup>4</sup>, Elisabeth Kutt<sup>5</sup>, Carol Record<sup>6</sup>, and**  
**Barbara Thomas<sup>7</sup>**

**Results**—Overall, 7893 women (14.6% of women the intervention arm and 18.1% of women attending at least one routine screen) experienced one or more false-positive screen during the trial. The rates of false-positive mammography at first and subsequent routine screens were 4.9% and 3.2%, respectively. The cumulative false-positive rate over seven screens was 20.5%. Eighty-nine percent of women who had a false-positive recall at their previous screen attended their next invitation to routine screening.

**Conclusions**—Rates of false-positive recall in the Age trial were comparable with the national screening programme, however, the positive predictive value of referral was lower. Experiencing a false-positive screen did not appear to lessen the likelihood of re-attendance in the trial.

**Impact**—The question of greatly increased false-positive rates in this age group and of their compromising re-attendance is refuted by the findings of this study.





# **Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy**

Eugenio Paci<sup>1</sup>, Guido Miccinesi<sup>1</sup>, Donella Puliti<sup>1</sup>, Paola Baldazzi<sup>2</sup>, Vincenzo De Lisi<sup>3</sup>, Fabio Falcini<sup>4</sup>, Claudia Cirilli<sup>5</sup>, Stefano Ferretti<sup>6</sup>, Lucia Mangone<sup>7</sup>, Alba Carola Finarelli<sup>8</sup>, Stefano Rosso<sup>9</sup>, Nereo Segnan<sup>10</sup>, Fabrizio Stracci<sup>11</sup>, Adele Traina<sup>12</sup>, Rosario Tumino<sup>13</sup> and Manuel Zorzi<sup>14</sup>

<sup>1</sup>Clinical and Descriptive Epidemiology Unit, CSPO, Research Institute of the Tuscany Region, via di San Salvi 12, Firenze, 50135, Italy

<sup>2</sup>ASL Bologna Area Nord, via Libert  45, 40016, San Giorgio di Piano, Bologna, Italy

<sup>3</sup>U.O. Oncologia, Azienda Ospedaliera-Universit , Parma Cancer Registry, via Abbeveratoia 4, Parma, 43100, Italy

<sup>4</sup>Dipartimento Interaziendale di Oncologia, Ospedale G.B. Morgagni–L. Pierantoni, Pad. Valsava, Romagna Cancer Registry, via C. Forlanini 34, Forl , 47100, Italy

<sup>5</sup>Modena Cancer Registry, via del Pozzo 71, Modena 41100, Italy

<sup>6</sup>Ferrara Cancer Registry, Dipartimento di Medicina Sperimentale e Diagnostica, Sezione di Anatomia, Istologia e Citologia Patologica, Universit  di Ferrara, v. Fossato di Mortara 64B, Ferrara, 44100, Italy

<sup>7</sup>Epidemiology Unit, Reggio-Emilia Cancer Registry, via Amendola 2, Reggio-Emilia, 42100, Italy

<sup>8</sup>Screening Programme, Emilia-Romagna Region Health Department, viale Aldo Moro 21, 40127, Bologna, Italy

<sup>9</sup>CPO – Piedmont Cancer Registry, via San Francesco da Paola 31, Torino, 10123, Italy

<sup>10</sup>CPO Piemonte, Epidemiology Unit, via San Francesco da Paola 31, Torino, 10123, Italy

<sup>11</sup>Umbria Cancer Registry, Dipartimento di specialit  Medico-Chirurgiche e Sanit  Pubblica, Universit  degli Studi di Perugia, via del Giochetto, Perugia, 06100, Italy

<sup>12</sup>Department of Oncology, ARNAS Ascoli, via Parlavechio 1, 90100, Palermo, Italy

<sup>13</sup>Department of Oncology 'Sebastiano Ferrara', Cancer Registry and Unit of Histopathology Azienda Ospedaliera 'Civile M.P. Arezzo', via Dante 109, Ragusa, 97100, Italy

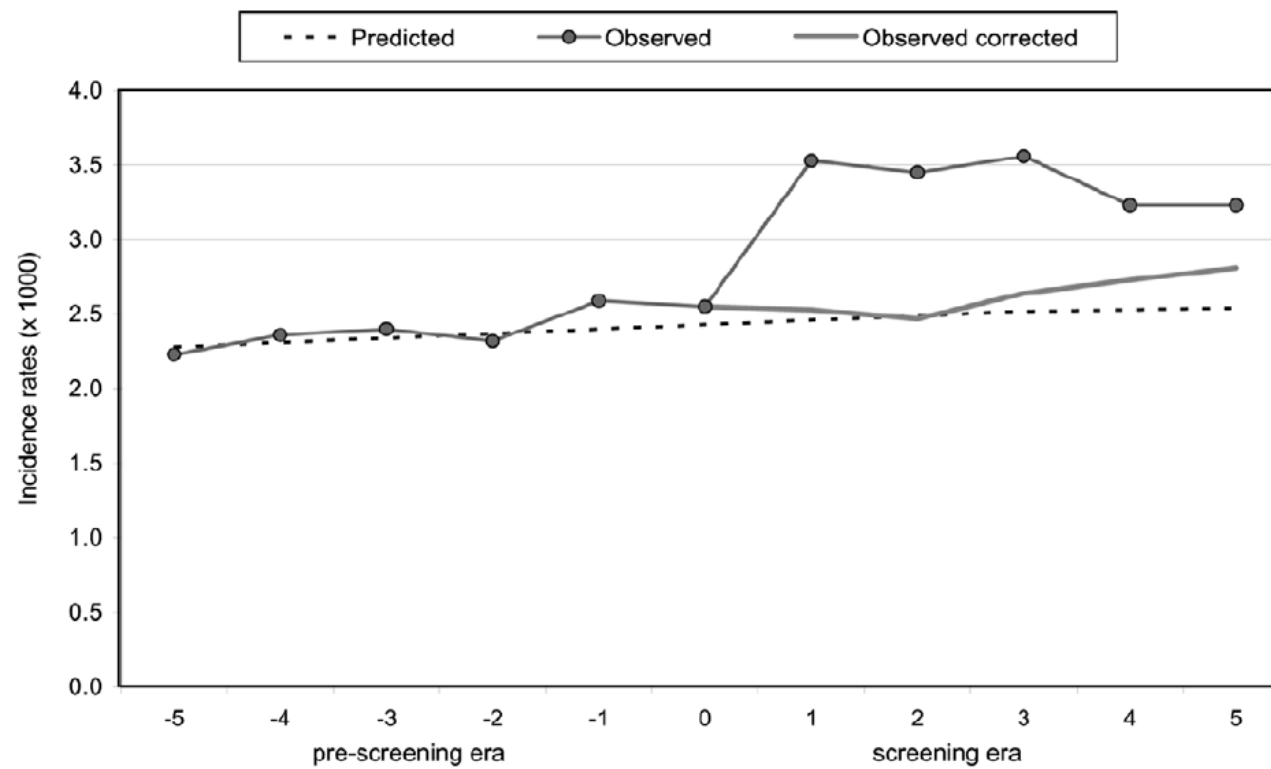
<sup>14</sup>Dipartimento di Scienze oncologiche e chirurgiche, Universit  degli Studi di Padova, Istituto Oncologico Veneto (IOV), via Gattamelata 64, Padova, 35128, Italy

Corresponding author: Eugenio Paci, e.paci@cspo.it

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*Breast Cancer Research* 2006, **8**:R68 (doi:10.1186/bcr1625)

**Figure 4**

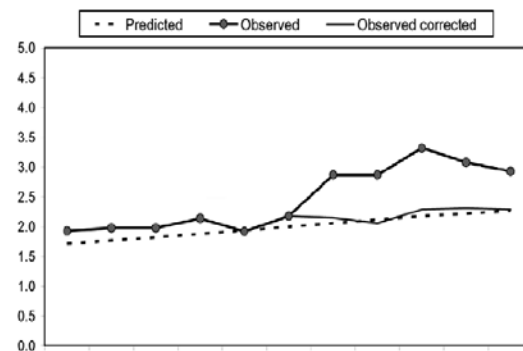


Breast cancer incidence rates predicted, observed, and observed corrected for lead time. The participants were aged 50 to 74 years.

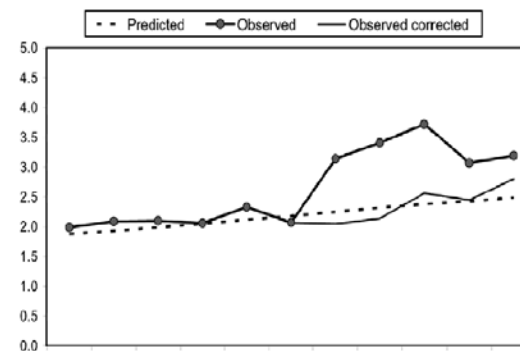


Figure 6

(a) 50-54

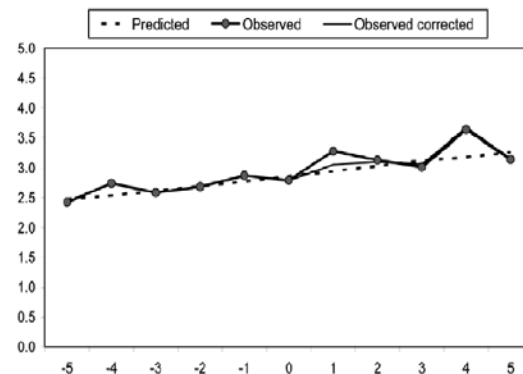


(b) 55-59



## Conclusion

In the screening age groups (ages 50 to 74 years) the excess of incidence was 36.2% and after correction for lead time the remaining excess of *in situ* and invasive carcinomas was 4.6% (95% CI 2 to 7%), less than 5%. Excluding *in situ* carcinomas the excess was 3.2% (95% CI 1 to 6%).



# Storia dello screening mammografico

Storia del cancro mammario

Le prove di efficacia dello screening

La diffusione dello screening

Le polemiche sullo screening

La nuova era dello screening: successi e sfide



# La nuova era dello screening: successi

- la prima generazione della storia che ha abbattuto la mortalità da cancro mammario (30-60%)
- un programma di sanità pubblica basato su prove di efficacia
- **equità**: offerta dei benefici a tutta la popolazione
- vantaggioso rapporto costo/beneficio e rischio beneficio
- efficacia / efficienza / monitoraggio / garanzia di qualità
- **contesto in cui si è sviluppata la collaborazione multidisciplinare**
- revisione continua e ricerca





# La nuova era dello screening: sfide



■ *Poichè sempre più spesso i tumori vengono scoperti mentre sono piccoli, entro i 14 mm di diametro, è imperativo che il trattamento sia adattato adeguatamente a questa nuova realtà*

*Questa Nuova Era richiede un nuovo  
approccio alla diagnosi e alla terapia  
di questa malattia*



# *Un impegno rinnovato*

■ *realizzare questi obiettivi non è facile*

*richiede nuove esperienze, un nuovo modo di pensare e un nuovo spirito di collaborazione e ricerca*

# La nuova era dello screening: sfide

- una parte delle aderenti allo screening muore ancora di cancro mammario (40% di mortalità non evitata nemmeno nelle aderenti)
- introduzione di nuove tecniche (superare il problema della densità)
- Introdurre nuovi protocolli su misura / basati sul rischio individuale
- ma sempre fondati su rigorosa valutazione scientifica
- valutando la sostenibilità del programma e i bilancio benefici / costi / effetti indesiderati
- stringere sempre più forti collaborazioni multidisciplinari
- ridurre il sovratrattamento
- revisione di tecniche, procedure, terminologie condivise
- stretta sinergia patologi-radiologi (alleanza degli iconologi)
- introduzione dell'intelligenza artificiale con liberazione di tempo clinico

# Storia dello screening mammografico

Alfonso Frigerio

