gis ma
gruppoitalianoscreening mammografico

WORKSHOP GISMa-ONS

18 maggio 2016

Lo screening nelle donne giovani: va cambiato qualcosa?

FINALBORGO
Complesso Monumentale di Santa Caterina
Auditorium

Nuove evidenze e nuove raccomandazioni

14.50 È tutto evidence-based nelle raccomandazioni internazionali?
P. Armaroli

15.10 Efficacia in pre-menopausa: UK Age Trial, valutazioni di efficacia e problemi aperti
E. Paci

15.30 La sovradiagnosi nelle donne giovani
D. Puliti

15.50 Discussione
Discussant: **P. Giorgi Rossi**

Eugenio Paci,
Epidemiologo,
Firenze

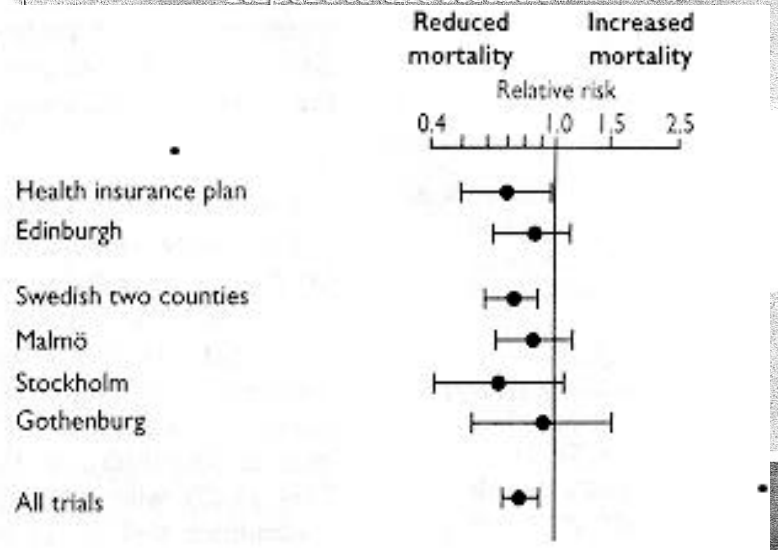
Una frattura tra USA e Europa che viene da lontano

Department of Health and Social Security

Women's Health Care

Breast Cancer Screening

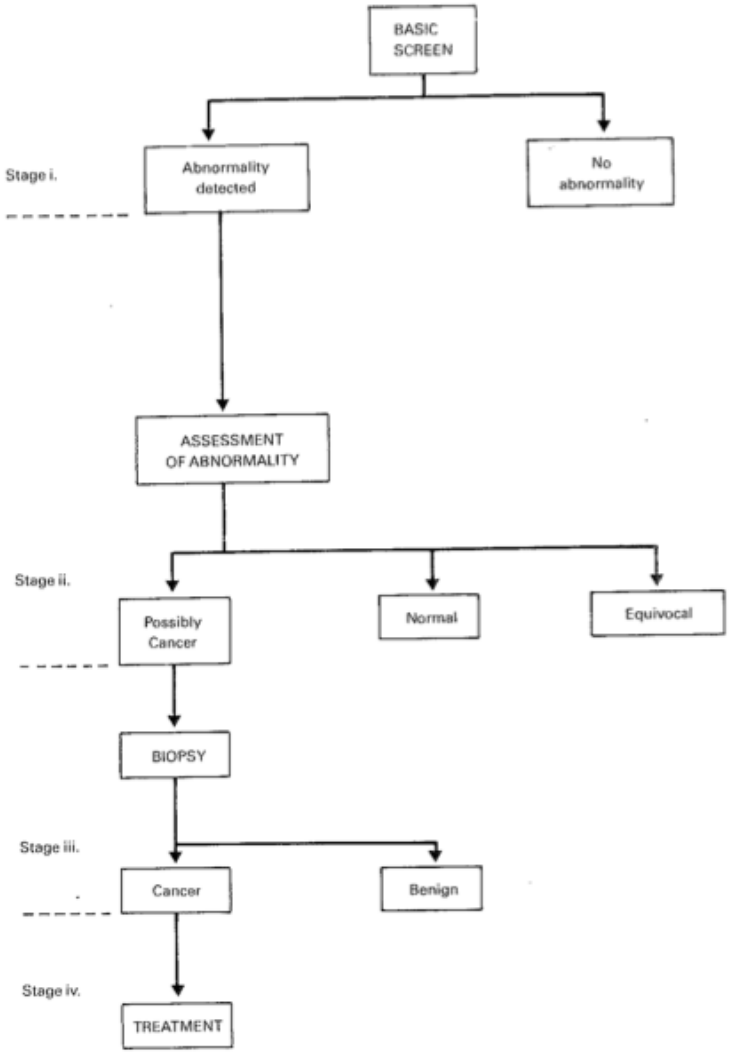
Report to the Health Ministers



1985-86

Her Majesty's Stationery Office

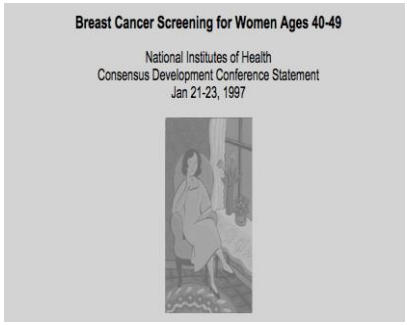
Figure 3.1 Screening Procedure



Notes: a) If the basic screen is single-view mammography stage i may include additional mammographic views.

b) Women with equivocal assessment results are kept under surveillance by the assessment team.

c) Normal at stage ii includes benign lesions considered insignificant.



"MAMMOGRAPHY SCREENING FOR WOMEN AGES 40-49"

Statement of

Richard D. Klausner, M.D.
Director, National Cancer Institute
on Screening Mammography

Before the

Subcommittee on Labor, Health and Human Services,
Education and Related Agencies
Senator Arlen Specter, Chairman
February 5, 1997

the balance and tone of the discussion in the Panel's draft report. It is my opinion that the draft report of the Panel overly minimizes the benefits and overly emphasizes the risks for this population. A balanced statement of the pros and cons of screening is essential for a woman to make an informed decision whether to initiate regular mammography in her forties.

	Screening interval (months)	CBE included	Study recruitment	Length of follow-up (years)	Age range at entry (years)	Relative risk of breast-cancer mortality (95% CI)
HIP[4]	12	Yes	1963–66	18	40–49	0·77 (0·53–1·11)
Ostergotland[3]	24	No	1978–81	17	38–49	1·05 (0·64–1·71)
Kopparberg[5]	24	No	1976–78	17	40–49	0·76 (0·42–1·40)
Malmo I[1]	18–24	No	1976–78	19	45–49	0·74 (0·44–1·25)
Malmo II[1]	18–24	No	1978–90	12·7	43–49	0·65 (0·39,1·08)
Gothenburg[3]	18	No	1982–84	13	39–49	0·56 (0·34–0·91)
Stockholm[2]	28	No	1981–83	15	39–49	1·52 (0·80–2·88)
Edinburgh[6]	24	Yes (annual)	1978–81	14	45–49	0·83 (0·54–1·27)
NBSS[7]	12	Yes	1980–85	12	40–49	0·97 (0·74–1·27)

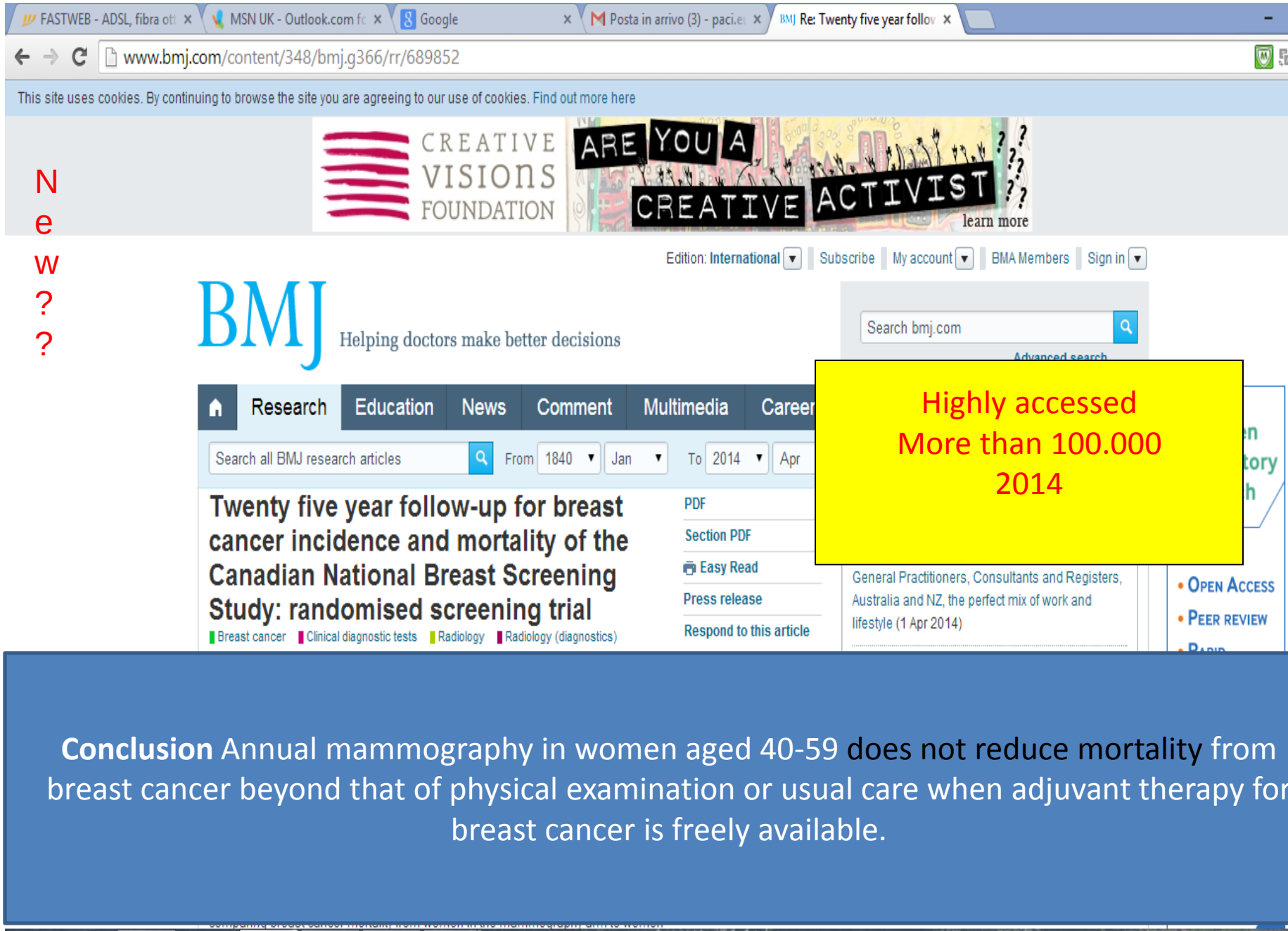
CBE=clinical breast examination.

Table 1: Randomised trials of breast screening in women younger than 50 years

Moss, 2006

Principali questioni relative all'efficacia:

- Assenza di stime statisticamente significative
- *Age creep*, cioè anticipazione di casi 'attribuiti' ai 50 anni.
- Eterogeneità tra i RCT (in particolare NBSS I, lo studio dedicato a rispondere alla questione delle40-49enni, presenta un risultato negativo)
- Minore incidenza e quindi basso VPP e alti costi. Rapporto costi/danni vs benefici critico


FASTWEB - ADSL, fibra ott
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Posta in arrivo (3) - paci.e
Re: Twenty five year follov
www.bmj.com/content/348/bmj.g366/rr/689852
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From 1840 Jan
To 2014 Apr
Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial
Breast cancer
Clinical diagnostic tests
Radiology
Radiology (diagnostics)
PDF
Section PDF
Easy Read
Press release
Respond to this article
Highly accessed
More than 100.000
2014
General Practitioners, Consultants and Registers, Australia and NZ, the perfect mix of work and lifestyle (1 Apr 2014)
Open Access
Peer review
Conclusion Annual mammography in women aged 40-59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available.

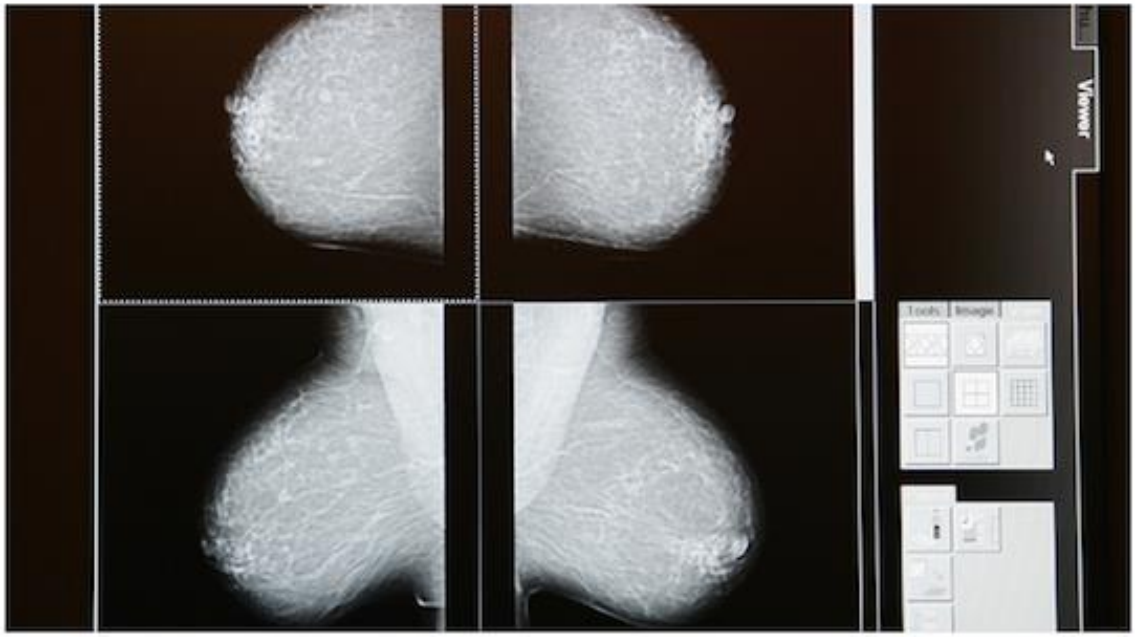
La mammografia funziona?

Un nuovo studio canadese ne mette in dubbio l'efficacia: dice che i programmi di
portato a diagnosi di tumori che non avrebbero dato conseguenze

301

93

6



Martedì 11 febbraio sul *British Medical Journal* è stato pubblicato uno studio sulla mammografia come strumento di diagnosi precoce per la prevenzione del tumore al seno. Si tratta di una ricerca che il *New York Times* ha definito come tra le «più ampie e meticolose mai fatte nei tempi recenti»: è stata condotta in Canada, ~~ha coinvolto 90 mila donne di età compresa tra 40 e 59 anni, è durata 25 anni e~~

IL POST

14 February 2014

New study?
Started in 1980, follow up at 13 years

The Quality of the Canadian Study (I and II) has been controversial since the first publication in 1990 because of the randomisation bias and quality of mammograms

Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial

Sue M Moss, Howard Cuckle, Andy Evans, Louise Johns, Michael Waller, Lynda Bobrow, for the Trial Management Group*

Summary

Background The efficacy of screening by mammography has been shown in randomised controlled trials in women Lancet 2006; 368: 2053–60

	Number of women	Women years	All cause deaths		Breast cancer deaths		Rate ratio (95% CI) intervention vs control group
			n	Rate per 1000 women years	n	Rate per 1000 women years	
Intervention	53 884	578 390	960	1·66	105	0·18	0·83 (0·66 – 1·04)
Control	106 956	1 149 380	1975	1·72	251	0·22	

Table 2: Mortality from all causes and from breast cancer in the intervention and control groups

Riduzione non significativa del 17% a 10 anni di follow up dalla randomizzazione (2006)

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,[1] Stefano Ciatto,[2] Alfonso Frigerio,[3] Carlo Naldoni,[4] Eugenio Paci,[2] Antonio Ponti,[5] Marco Rosselli del Turco,[2] Marcello Vettorazzi,[6] Marco Zappa[2]

Epidemiologia& Prevenzione, 2007

Tabella 3. Mortalità da carcinoma mammario nel braccio di screening rispetto a quello di controllo (odds ratio = OR; intervallo di confidenza al 95% = IC) in trial clinici randomizzati che includevano donne di 40-49 anni all'arruolamento.

Table 3. Breast cancer mortality in screening as compared to control arm (odds ratio = OR; 95% confidence interval = IC) in randomized clinical trials including women aged 40-49 years at entry.

Studio	frequenza di screening (mesi)	classe di età	fo		
HIP, 63-66	12	40-59			
Ostergotland 78-81	24	38-49			
Kopparberg, 76-78	24	40-49			
Malmo I 76-78	18-24	45-49			
Malmo II, 78-90	18-24	43-49			
Gothenburg, 82-84	18	39-49			
Stockholm, 81-83	28	39-49	15	1,52	0,80-2,88
Edinburgh, 78-81	24	45-49	14	0,83	0,54-1,27
NBSS I, 80-85	12	40-49	12	0,97	0,74-1,27

Modificato da Moss, 2004[3]

Intervallo	1° anno	2° anno	3° anno
Firenze			
40-49	0,24	0,41	0,98
50-59	0,17	0,45	0,51
60-69	0,09	0,17	0,39
Trial svedesi			
40-49	0,37	0,67	0,60
50-59	0,11	0,29	0,46
60-69	0,14	0,28	0,43

Modificato da Paci et al.15

Tabella 5. Rapporto tra tasso osservato di carcinoma d'intervallo rispetto a tasso di incidenza atteso in assenza di screening: evidenze dal programma di screening di Firenze e dai trial svedesi, per classi di età e anno di intervallo.

Table 5. Ratio of observed interval cancer rate as compared to expected incidence rate in absence of screening: evidence from the Florence programme and from Swedish trials, by age and year of interval.

Maggiore intensità di screening. La questione età rimane per molti aspetti aperta, non ultimo dal punto di vista del rapporto costi/danni vs beneficio.

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

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Riassunto

Il Gruppo italiano per lo screening mammografico (GISMa) ha organizzato una conferenza di consenso nazionale, invitando un elevato numero di esperti nei vari campi relazionati allo screening, con lo scopo finale di produrre un documento di consenso che potesse divenire lo standard di riferimento per l'Italia. Il documento di consenso conclude che la copertura completa del territorio nazionale mediante programmi di screening organizzato per il carcinoma della mammella (età 50-69), colon-rettale e cervicale resta un obiettivo prioritario, prima che sia presa in considerazione l'estensione dello screening mammografico organizzato a fasce di età inferiori e superiori. Ove siano disponibili le risorse necessarie, è raccomandata l'estensione dello screening mammografico fino ai 74 anni di età, almeno per coloro che hanno regolarmente partecipato allo screening fino ai 69 anni. Può essere presa in considerazione l'estensione dello screening organizzato alla fascia di età 40-49 a patto che siano disponibili le risorse necessarie, si adotti un intervallo di screening annuale, si fornisca alle donne una congrua informazione relativa ai pro e ai contro dello screening e si dia la priorità alla fascia di età 45-49.

(*Epidemiol Prev* 2007; 31(1): XXX-XXX)

Parole chiave: carcinoma mammario, screening, mammografia

Clinical Review & Education

Review

A Systematic Assessment of Benefits and Risks to Guide Breast Cancer Screening Decisions

Lydia E. Pace, MD, MPH; Nancy L. Keating, MD, MPH

Table 1. Pooled Results from Randomized Clinical Trials on Mortality Reductions With Mammography Screening by Age Group

Age, y	No. of Studies	Total Events in Group/Total No.		RR (95% CI) With Mammography Screening[9]	ARR With Mammography Screening	NNI to Screening[9]
		Invited Group	Control Group			
39-49	8[8,10-14]	448/152 300	625/195 919	0.85 (0.75 0.96)	0.0005	1904
50-59	6[11,13-15]	361/78 465	410/69 849	0.86 (0.75-0.99)	0.0007	1339
60-69	2[13]	110/19 093	155/18 377	0.68 (0.54- 0.87)	0.0027	377
70-74	1[13]	42/5073	36/4859	1.12 (0.73-1.72)	NA	NA

Abbreviations: ARR, adjusted risk ratio; NA, not available; NNI, number needed to invite; RR, risk ratio.

La minore efficacia e il minor rapporto benefici/danni nelle donne
in premenopausa era stato identificato sin dallo studio HIP (1969)
e fu la ragione dell'avvio delllo Studio Canada I e poi dell'UK AGE TRIAL

Jama, 2014

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[1]; Stephen W. Duffy, MSc[2]; Shahin Abdsaleh, MD, PhD[3]; Lena Björneld, RN[4]; Pál Bordás, MD[5]; László Tabár, MD, PhD[6]; Bedrich Viták, MD, PhD[7]; Sophia Zackrisson, MD, PhD[8]; Lennarth Nyström, PhD[9]; and Håkan Jonsson, PhD[1]

BACKGROUND: The effectiveness of mammography screening for women ages 40 to 49 years still is questioned, and few studies of the effectiveness of service screening for this age group have been conducted. **METHODS:** Breast cancer mortality was compared between women who were invited to service screening at ages 40 to 49 years (study group) and women in the same age group who were not invited during 1986 to 2005 (control group). Together, these women comprise the Mammography Screening of Young Women (SCRY) cohort, which includes all Swedish counties. A prescreening period was defined to facilitate a comparison of mortality in the absence of screening. The outcome measure was refined mortality, ie, breast cancer death for women who were diagnosed during follow-up at ages 40 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*** **2011;117:714–22.** *© 2010 American Cancer Society.*

KEYWORDS: mammography, screening, breast cancer, mortality.

Original Article

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[1]; Stephen W. Duffy, MSc[2]; Shahin Abdsaleh, MD, PhD[3]; Lena Björneld, RN[4]; Pál Bordás, MD[5]; László Tabár, MD, PhD[6]; Bedrich Viták, MD, PhD[7]; Sophia Zackrisson, MD, PhD[8]; Lennarth Nyström, PhD[9]; and Håkan Jonsson, PhD[1]

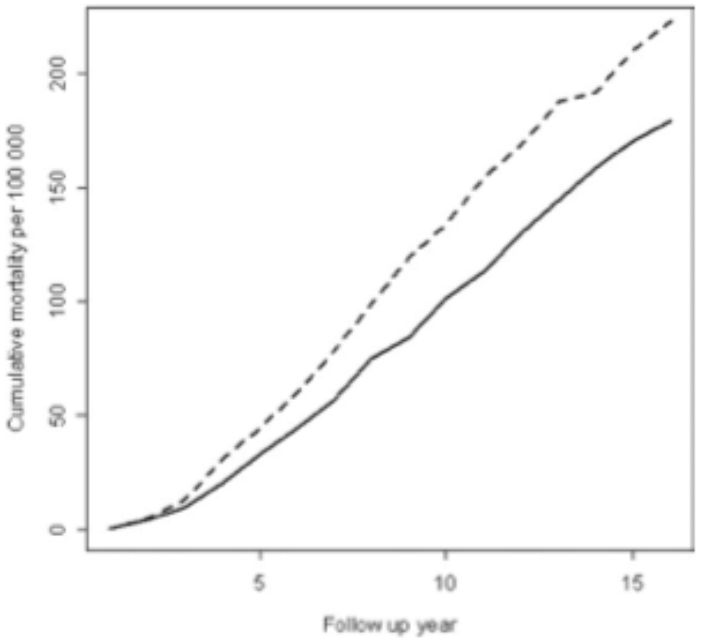


Figure 2. This chart illustrates the crude cumulative breast cancer mortality per 100,000 person-years. Solid line indicates the study group; dashed line, control group.

Figure 1. This is a simplified map of the areas that were included in the study group and the control group.

Handbook 15 –IARC WHO Prevention Monograph.
Publication is expected . Based on a worldwide review.

Evaluation of breast cancer screening with mammography

Age range (years)	Reduction in breast cancer mortality	
	Efficacy	Effectiveness
40–44	*Inadequate*	*Limited*
45–49		*Limited*
50–69	*Sufficient*	*Sufficient*
70–74	*Inadequate*	*Sufficient*
Optimal screening interval	*Inadequate*	*No data*

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Breast-Cancer Screening — Viewpoint of the IARC Working Group

Béatrice Lauby-Secretan, Ph.D., Chiara Scoccianti, Ph.D., Dana Loomis, Ph.D., Lamia Benbrahim-Tallaa, Ph.D., Véronique Bouvard, Ph.D., Franca Bianchini, Ph.D., and Kurt Straif, M.P.H., M.D., Ph.D., for the International Agency for Research on Cancer Handbook Working Group

Annals of Internal Medicine

CLINICAL GUIDELINE

Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement

Albert L. Siu, MD, MSPH, on behalf of the U.S. Preventive Services Task Force

Description: Update of the 2009 U.S. Preventive Services Task Force (USPSTF) recommendation on screening for breast cancer.

Methods: The USPSTF reviewed the evidence on the following: effectiveness of breast cancer screening in reducing breast cancer–specific and all-cause mortality, as well as the incidence of advanced breast cancer and treatment-related morbidity; harms of breast cancer screening; test performance characteristics of digital breast tomosynthesis as a primary screening strategy; and adjunctive screening in women with increased breast density. In addition, the USPSTF reviewed comparative decision models on optimal starting and stopping ages and intervals for screening mammography; how breast density, breast cancer risk, and comorbidity level affect the balance of benefit and harms of screening mammography; and the number of radiation-induced breast cancer cases and deaths associated with different screening mammography strategies over the course of a woman's lifetime.

Population: This recommendation applies to asymptomatic women aged 40 years or older who do not have preexisting breast cancer or a previously diagnosed high-risk breast lesion and who are not at high risk for breast cancer because of a known underlying genetic mutation (such as a *BRCA1* or *BRCA2* gene mutation or other familial breast cancer syndrome) or a history of chest radiation at a young age.

Recommendations: The USPSTF recommends biennial screening mammography for women aged 50 to 74 years. (B recommendation)

The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years. (C recommendation)

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women aged 75 years or older. (I statement)

The USPSTF concludes that the current evidence is insufficient to assess the benefits and harms of digital breast tomosynthesis (DBT) as a primary screening method for breast cancer. (I statement)

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adjunctive screening for breast cancer using breast ultrasonography, magnetic resonance imaging (MRI), DBT, or other methods in women identified to have dense breasts on an otherwise negative screening mammogram. (I statement)

Ann Intern Med. doi:10.7326/M15-2886 **www.annals.org**

For author affiliation, see end of text.

This article was published at www.annals.org on 12 January 2016.

* For members of the USPSTF, see the **Appendix** (available at

Clinical Review & Education

Special Communication

Breast Cancer Screening for Women at Average Risk
2015 Guideline Update From the American Cancer Society

Kevin C. Oeffinger, MD; Elizabeth T. H. Fontham, MPH, DrPH; Ruth Etzioni, PhD; Abbe Herzig, PhD; James S. Michaelson, PhD; Ya-Chen Tina Shih, PhD; Louise C. Walter, MD; Timothy R. Church, PhD; Christopher R. Flowers, MD, MS; Samuel J. LaMonte, MD; Andrew M. D. Wolf, MD; Carol DeSantis, MPH; Joannie Lortet-Tieulent, MSc; Kimberly Andrews; Deana Manassaram-Baptiste, PhD; Debbie Saslow, PhD; Robert A. Smith, PhD; Otis W. Brawley, MD; Richard Wender, MD

- **Una svolta importante che sposta la valutazione dall'efficacia a potenziali benefici, limiti e danni associati allo screening.**
- **La raccomandazione *forte* è di iniziare lo screening a 45 anni.**
- **Annuale fino a 54 e poi biennale fino a che vi è una attesa di vita di 10 anni o più.(*Qualificata*, dipende da valori e preferenze sul rischio beneficio)**
- **Opportunità di fare screening mammografico annuale tra i 40-44 (*Qualificata*)**
- **Non vien più raccomandato l'esame clinico del seno (CBE) come screening per le donne a rischio medio , ad alcuna età.(*Qualificata*)**

Box 2. American Cancer Society Guideline for Breast Cancer Screening, 2015

These recommendations represent guidance from the American Cancer Society (ACS) for women at average risk of breast cancer: women without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer (eg, *BRCA*), or a history of previous radiotherapy to the chest at a young age.

The ACS recommends that all women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.

Recommendations[a]

1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. (*Strong Recommendation*)
   1a. Women aged 45 to 54 years should be screened annually. *(Qualified Recommendation)*
   1b. Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. *(Qualified Recommendation)*
   1c. Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. *(Qualified Recommendation)*
2. Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. *(Qualified Recommendation)*
3. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age. *(Qualified Recommendation)*

[a] A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. Qualified recommendations indicate there is clear evidence of benefit of screening but less certainty about the balance of benefits and harms, or about patients' values and preferences, which could lead to different decisions about screening.[12,13]

Effect of mammographic screening from age 40 years on breast cancer mortality in the UK Age trial at 17 years' follow-up: a randomised controlled trial

Sue M Moss, Christopher Wale, Robert Smith, Andrew Evans, Howard Cuckle, Stephen W Duffy

Summary

Background Age-specific effects of mammographic screening, and the timing of such effects, are a matter of debate. The results of the UK Age trial, which compared the effect of invitation to annual mammographic screening from age 40 years with commencement of screening at age 50 years on breast cancer mortality, have been reported at 10 years of follow-up and showed no significant difference in mortality between the trial groups. Here, we report the results of the UK Age trial after 17 years of follow-up.

Lancet Oncol 2015

Published Online July 21, 2015

http://dx.doi.org/10.1016/S1470-2045(15)00128-X

See Online/Comment http://dx.doi.org/10.1016/

Interpretation Our results support an early reduction in mortality from breast cancer with annual mammography screening in women aged 40–49 years. Further data are needed to fully understand long-term effects. Cumulative incidence figures suggest at worst a small amount of overdiagnosis.

Questione:

La Mammografia di Screening annuale, iniziata a 40 anni e proseguita fino a 47 anni (quando inizia l'attuale offerta attiva di screening in UK) , riduce la mortalità specifica per causa?

17 anni

	Number of women	0–10 years after randomisation					More than 10 years after randomisation				
		Women-years*	Breast cancer deaths	Rate per 1000 women-years	Rate ratio (95% CI)	Absolute risk reduction per 1000 women (95% CI)	Women-years†	Breast cancer deaths	Rate per 1000 women-years	Rate ratio (95% CI)	Absolute risk reduction per 1000 women (95% CI)
Intervention	53 883	532 747	83	0·156	0·75 (0·58 to 0·97)	0·51 (0·08 to 0·94)	408 221	99	0·243	1·02 (0·80 to 1·30)	−0·03 (−0·47 to 0·41)
Control	106 953	1 058 322	219	0·207	1·0	..	810 395	193	0·238	1·0	..

*Calculated from date of randomisation to 10 years after randomisation or end of follow-up, whichever was earliest; median follow-up of 10·0 years (IQR 9·9–10·0). †Calculated from 10 years after randomisation to end of follow-up. Median follow-up of 7·7 years (IQR 6·9–8·9).

Table 1: Mortality from breast cancers diagnosed during the intervention phase by time since randomisation

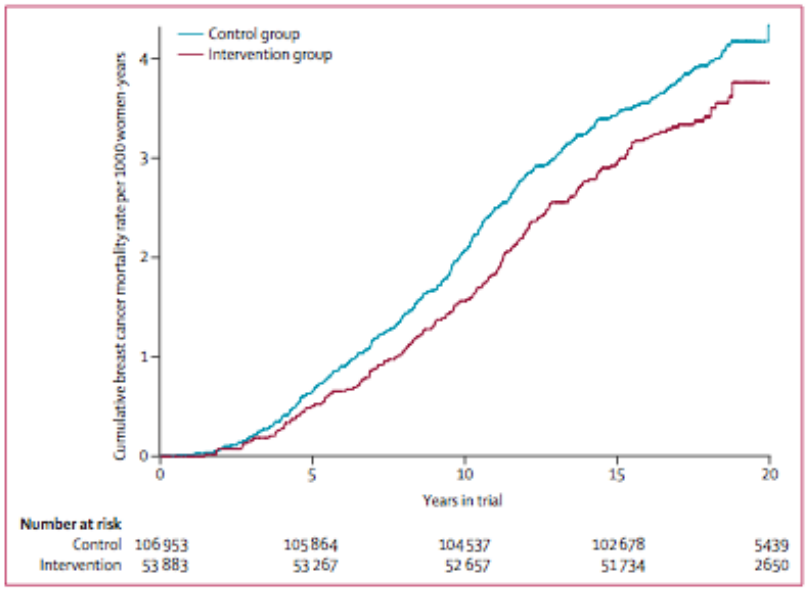


Figure 2: Nelson-Aalen estimate of cumulative breast cancer mortality (restricted to deaths from breast cancers diagnosed in the intervention phase)

Follow up ristretto ai decessi che originano dai tumori della mammella
Diagnosticati (allo screening o clinicamente) nella fase di intervento (7 anni)

Riduzione della mortalità per causa statisticamente significativa del 25%
Differenza assoluta circa 5 decessi ogni 10.000 donne seguite 10 anni.

2nda Domanda, che richiede un modello statistico di simulazione

- Cosa aggiunge in termini di efficacia (e anche di rapporto costi- danni/benefici) lo screening nelle donne in premenopausa?

	Intervention			Control			Rate ratio (95% CI)	Absolute reduction per 1000 women-years (95% CI)	Absolute risk reduction per 1000 women (95% CI)
	Women-years*	n	Rate per 1000 women-years	Women-years	n	Rate per 1000 women-years			
0–4 years	267 864	27	0·10	532 104	69	0·13	0·78 (0·50 to 1·21)	0·03 (−0·02 to 0·08)	0·14 (−0·10 to 0·39)
5–9 years	264 884	56	0·21	526 220	152	0·29	0·73 (0·54 to 0·99)	0·08 (0·006 to 0·15)	0·38 (0·03 to 0·74)
10–14 years	261 163	98	0·38	518 223	185	0·36	1·05 (0·82 to 1·34)	−0·02 (−0·11 to 0·07)	−0·09 (−0·54 to 0·36)
More than 15 years	147 057	61	0·41	292 170	109	0·37	1·11 (0·81 to 1·52)	−0·04 (−0·17 to 0·08)	−0·12 (−0·47 to 0·24)
Total	940 969	242	0·257	1 868 717	515	0·276	0·93 (0·80 to 1·09)	0·02 (−0·02 to 0·06)	0·32 (−0·38 to 1·02)

Rate ratio and absolute risk reduction are for intervention versus control group. *Women-years in each time period from randomisation.

Table 3: Breast cancer mortality by period in trial

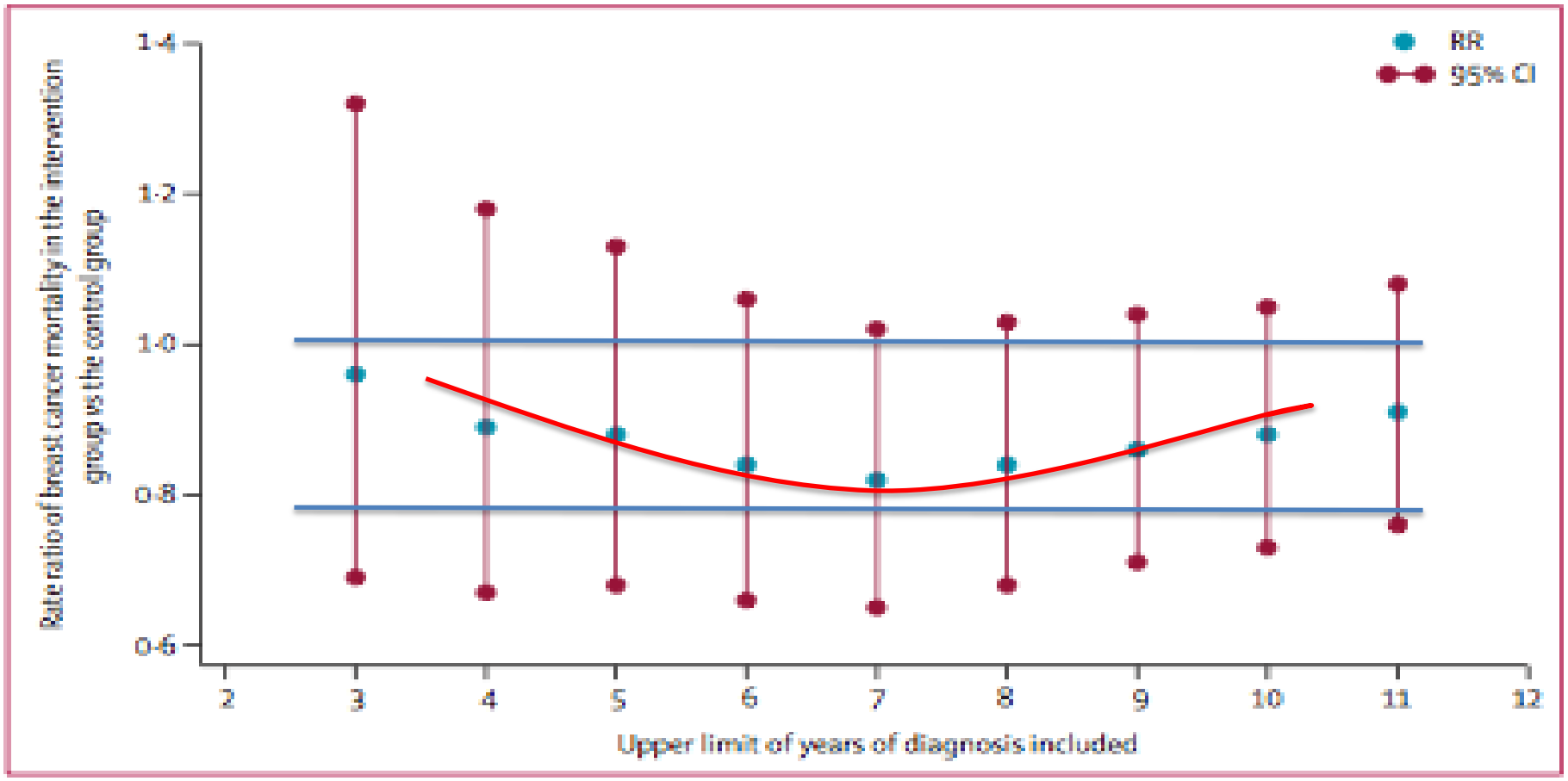


Figure 4: Rate ratio of breast cancer mortality in the intervention group, according to period of diagnosis of breast cancer

L'analisi per anno di diagnosi del tumore mammario mostra come il Rischio Relativo traprobabilità di morte per tumore mammario nel gruppo di intervento verso il gruppo di controllo diminuisce fino al 7 anno e poi torna verso 1, perchè l'esposizione allo screening diviene uguale nei due gruppi dai 47 anni in avanti (UK)

UK AGE TRIAL, Lancet Oncology, 2015
Decessi per TM x 10.000 donne seguite per 17 anni

Intervento	Controllo	RR	DIFF
Anni Follow up	0-9 anni		
16	21		
		-25%	-5

Percentuale dei decessi controlli

TUTTE 5/57=9%

SOLO SCREENING 5/45=11%

BREAST CANCER

Doubtful health benefit of screening from 40 years of age

Philippe Autier

Refers to Moss, S. M. *et al.* Effect of mammographic screening from age 40 years on breast cancer mortality in the UK Age trial at 17 years' follow-up: a randomised controlled trial. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(15)00128-X

Results of the UK Age trial suggest a significant benefit of annual mammography initiated at 39–41 years of age in preventing breast-cancer deaths occurring before the age of 50 years; however, this approach had no effect on the risk of breast-cancer death occurring before the age of 60 years and leads to prolonged deteriorations in quality of life owing to overdiagnosis.

Table 1 | Rates and relative risks of breast-cancer mortality in the UK Age trial*

Breast-cancer deaths considered	Number of breast-cancer deaths		Women-years		Breast-cancer-death rate per 1,000 women-years		Relative risk of breast cancer death (95% CI)	Rate difference per 1,000 women-years (intervention vs control group)
	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group		
In women diagnosed <10 years after randomization								
Within 10 years	83	219	532,747	1,058,322	0.156	0.207	0.75 (0.58–0.97)	–0.051
Beyond 10 years	99	193	408,221	810,395	0.243	0.238	1.02 (0.80–1.30)	0.005
Up to year 20	182	412	940,969	1,868,717	0.193	0.220	0.88 (0.74–1.04)	–0.027
In women diagnosed ≥10 years after randomization‡								
Beyond 10 years	60	103	408,221	810,395	0.147	0.127	1.16 (0.84–1.59)	0.020
In all women diagnosed up to year 20 after randomization								
Up to year 20	242	515	940,969	1,868,717	0.257	0.276	0.93 (0.80–1.09)	–0.018

*All data come from the publication by Moss et al.[1] ‡Figures calculated based on data from Moss et al.[1]

Anni 7 - 9

(Table 1). Nevertheless, this result indicates that a persistent excess of deaths in the intervention group during this period contributed to equalizing death rates in the two groups at year 20. These observations echo those of previous studies, which concluded that annual mammographic screening of women in their forties would result in an increase in breast-cancer mortality.[6–8] In particular, periodic exposure of the breasts to X-rays starting at age 39–41 years in the UK Age trial might have increased the risk of breast-cancer death at the later time points.

Moss S., Lancet Onc. 2015

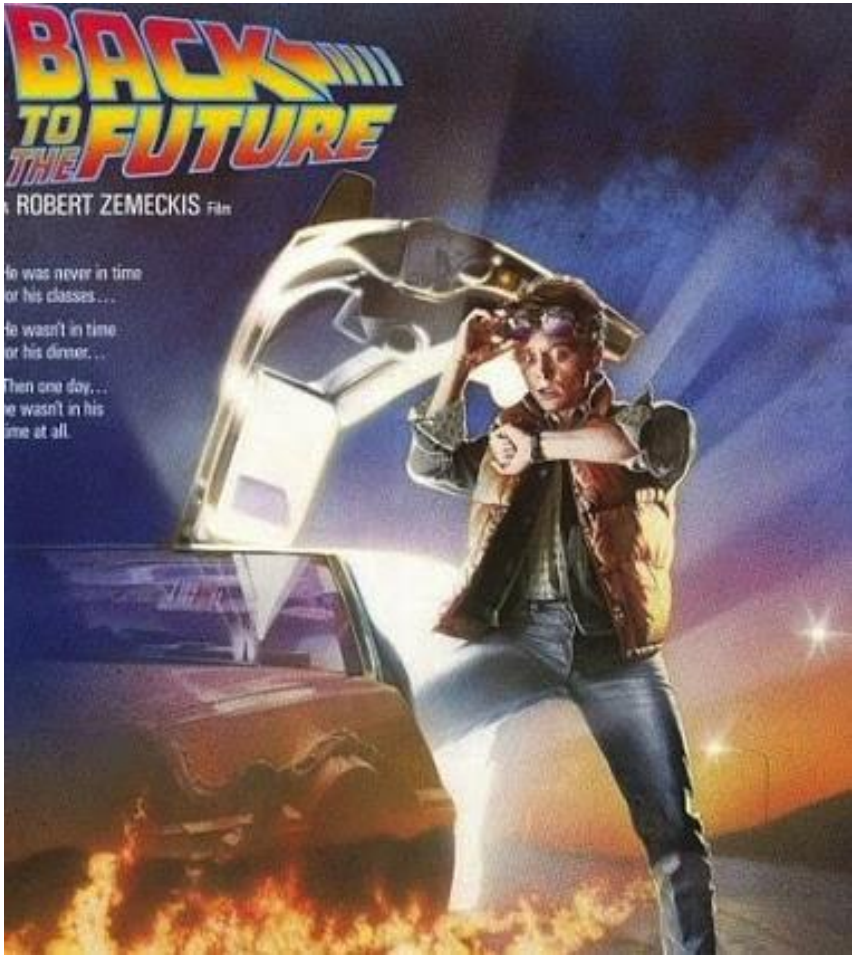
The reported difference in breast cancer mortality peaked when the analysis was restricted to breast cancers diagnosed up to 7 years of follow-up, despite the fact that at this point in time, there was an excess of breast cancer incidence in the intervention group, which would tend to introduce a bias against screening as some of this excess will be due to the effect of lead time—ie, the analysis includes deaths from cancers in the intervention group whose equivalent in the control group are excluded because they will be diagnosed after the 7 year period. The dilution of effect seen in figure 4 as breast cancers diagnosed beyond year 7 or 8 are included represents the fact that the two groups have essentially the same screening regimen from this point in time.

The difference between the long-term effect restricted to deaths from cancers diagnosed in the intervention phase and that reported in table 3 including all cancers irrespective of period of diagnosis shows how a reduction in mortality with screening can be obscured by the inclusion of deaths from cancers diagnosed outside the screening period. This observation further casts doubt on some negative results of analyses of published mortality rates that include deaths from cancers diagnosed outside the screening period—ie, cancers that could not have been affected by the intervention.[15,16]

La riduzione di mortalità tra le donne che ricevono lo screening a 40+ è oscurata dalla inclusione di morti per TM diagnosticati al di fuori del periodo di screening

La differenza tra l'effetto a lungo termine nelle morti ristrette a quelle nella sola fase di intervento (40-47) e quelle che includono tutte le donne diagnosticate senza tenere conto del periodo di diagnosi oscura l'effetto dello screening eseguito prima, in presenza di una non differenza di screening, dopo i 47, tra gruppo di intervento e gruppo di controllo

Back to the future



- Bisognerebbe tornar indietro e cambiare l'atteggiamento di chi non appoggiò le proposte di studi longitudinali di screening su donne 40-41 anni *at entry,* nella consapevolezza di quanto danno è stato fatto alla conoscenza del tumore della mammella nelle donne in premenopausa

Considerazioni

- L’estensione alle donne in premenopausa è prevalentemente motivata dalla opportunità di una offerta di Sanità Pubblica e un recupero delle donne al servizio di screening.
- Lo sforzo di prevedere l’offerta di screening annuale è notevole
- La necessità di giustificare in termini di riduzione della mortatlità l’estensione dello screening organizzato esiste e le Regioni dove è stato avviato sono importanti laboratori osservazionali

Scelte

- La valutazione sullo screening in premenopausa richiede scelte non solo numeriche (vite salvate vs danni/benefici).
- La questione etica riguarda in questo caso anche la rilevanza delle morti premature (che pesano nel complesso poco sul totale delle morti per tumore mammario) .
- In RER con 130.000 70% di adesione) donne tra i 45-49 è ipotizzabile un impatto in 10 anni di circa 65 morti premature evitate per ogni coorte di 45 anni.

RegioneEmilia-Romagna

Age Group	N	% of the age group/total regional target population	Interval
45-49	163.354	19.5	1 year
50-69	548.855	65.4	2 years (started in 1996)
70-74	126.311	15.1	2 years
TOT 45-74	**838.520**	**100.0**	

5x33(000)X0.7= 115

Regional Participation rate 45-49 : 62.7% (2010) 71% (2011)

Epidemiology Biostatistics and Public Health - 2014, Volume XX, Number X

ORIGINAL ARTICLES

ebph

Comparison of multi-state Markov models for cancer progression with different procedures for parameters estimation. An application to breast cancer

Leonardo Ventura[1], Giulia Carreras[1], Donatella Puliti[1], Eugenio Paci[1], Marco Zappa[1], Guido Miccinesi[1]

Il modello consente di valutare scenari di impatto di nuovi interventi, ed è basato su dati Italiani e atttuali

Cosa è necessario fare
Studi di comparative effectiveness (Impatto)

- Studio di coorti per valutare l'impatto (pre/post inizio programma) sia sull'incidenza, mortalità sia l'effetto addittivo dell'inizio anticipato.
- Studi coorte/caso controllo per valutare specifiche condizioni come SES , parità e livelli di rischio(Cancer , 2015 , studio SCRY per SES)
- Valutazione con Modelli di predizione (vedi Ventura, 2015)

Estensione dello screening e ricerca nelle donne in premenopausa

- La possibilità di ricerca e intervento con iniziative integrate sugli stili di vita (Obesità, Sindrome Metabolica, …) deve essere valutata per essere inserita nei programmi di sanità pubblica.
- L'estensione dello screening alle donne 45-49 (54) deve essere accompagnata dalla ricerca su i rapporti tra età, genetica, densità (TBST) e caratteristiche dei tumori.
- La ricerca è' essenziale in presenza di una evidenza limitata di efficacia ed è correlata al bisogno di capire i limiti dello screening e le necessarie integrazioni alla mammografia di screening
- La possibilità di intervento non deve dimenticare le donne che non sono raggiunte/o necessitano maggiormente di sorveglianza (altre fasce di età, alto rischio)

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COMMENTARY

How Many Etiological Subtypes of Breast Cancer: Two, Three, Four, Or More?

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Manuscript received August 15, 2013; revised May 1, 2014; accepted May 13, 2014.

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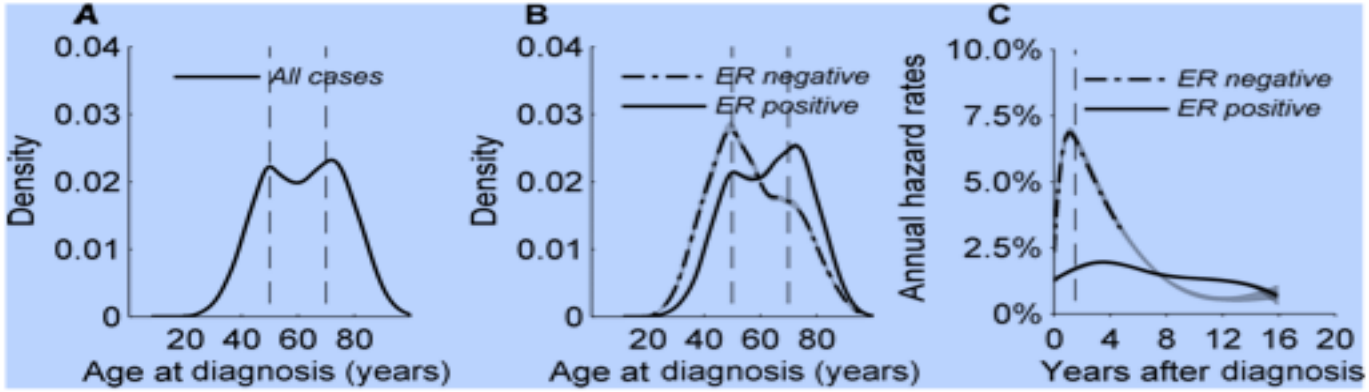

Figure 2. Invasive female breast cancer case data were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results 9 Registries Database from 1990 through 2010 database overall and for estrogen receptor (ER)–positive and ER-negative cancers. Bimodal breast cancer populations have fluctuated over time likely because of complex interactions between age-related biologic, risk factor, and screening phenomena, as previously described (186). For illustration, this figure has been restricted to the 1995 to 1998 period, during which a bimodal female breast cancer population was evenly distributed between early-onset and late-onset subtypes. Age distributions at diagnosis (or density plots) with 95% confidence intervals were constructed in 1-year age increments using a kernel density estimator applied to the corresponding age-at-diagnosis frequency histogram. The area under the curve represents 100% of the cancer records. The vertical axis shows the smoothed distribution (or proportion) with the frequency value × 100 = percentage distribution. **A)** Density plot for breast cancer overall demonstrates a bimodal age distribution at diagnosis with the modal ages near 50 and 70 years representing the central tendencies for early-onset and late-onset breast cancers. **B)** Density plot for ER-negative tumors also shows a bimodal age distribution at diagnosis with a dominant early-onset mode near age 50 years and a minor mode around age 70 years. Density plot for ER-positive tumors shows bimodal age distributions at diagnosis with a dominant late-onset mode near age 70 years and a minor mode around age 50 years. **C)** The risk for breast cancer–specific death can be expressed as an annual hazard rate, which describes the instantaneous rate of dying from breast cancer in a specified time interval (ie, percentage dying per year) after diagnosis among women who are alive at the beginning of that time interval. Nonparametric hazard function estimators were applied that modeled the hazard profile of ER-positive and ER-negative cancers, allowing both the shape and magnitude to be estimated free of ad hoc mathematical assumptions. Specifically, the hazard rate curves were generated using cubic splines with joinpoints selected by Akaike's information criteria and 95% confidence intervals applied with bootstrap resampling (187–189). Bimodal age distributions at diagnosis among women (**B**) are associated with two very different cancer-specific outcomes. ER-negative hazards for breast cancer death peak near 7.5% per year approximately 2 years after initial diagnosis and then decline rapidly. ER-positive hazards lack a sharp peak but are relatively constant at 1% to 2% per year. Falling ER-negative and constant ER-positive hazards cross over approximately 8 years after breast cancer diagnosis.