Cancro della mammella

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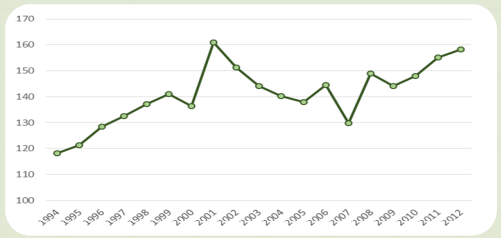
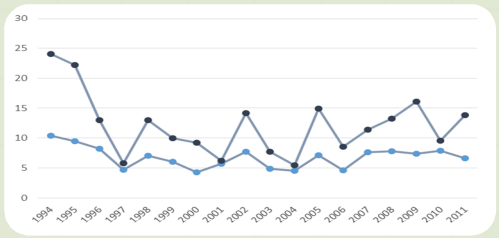
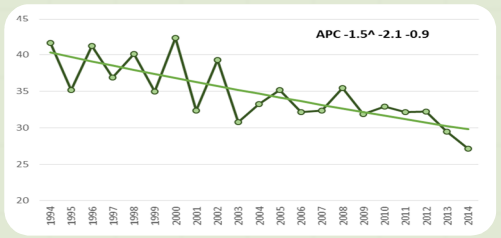
Dip. Medicina Sperimentale

Epidemiologia del carcinoma della mammella







Incidenza ↑

Fattori di rischio

Screening

Severità ↘

Screening

Mortalità ↘

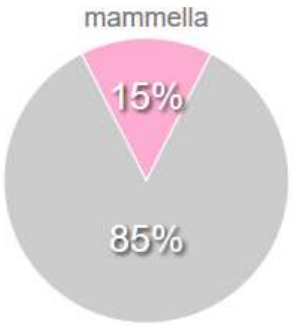
Trattamento

Screening

Prima causa di morte per tumore maligno nel sesso femminile

1763 casi nel periodo 2004-2013

In media 176 casi per anno

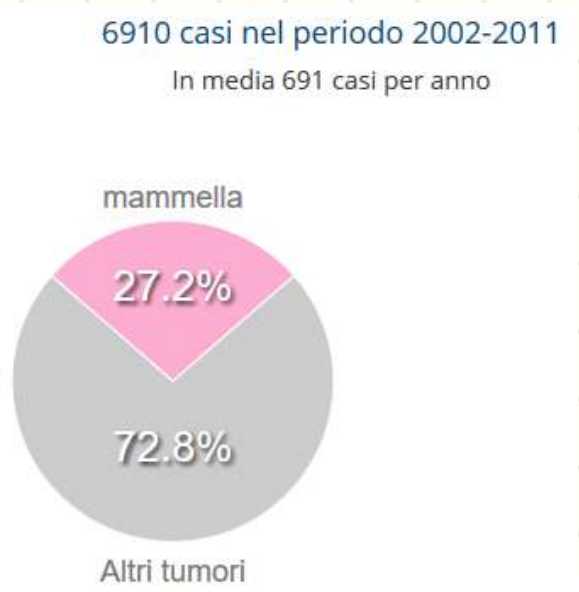


Prime cinque cause di morte per tumore più frequenti e proporzione sul totale dei decessi oncologici per sesso.

Periodo completo: 1994 - 2013 | **Ultimi 10 anni: 2004 - 2013** | Ultimi 5 anni: 2009 - 2013

Rank	Maschi	Rank	Femmine	Rank	Tutta la popolazione
1	**Bronchi e polmoni** 369 casi per anno - 23.7%	1	**Mammella** 176 casi per anno - 15.0%	1	**Bronchi e polmoni** 487 casi per anno - 17.8%
2	**Colon retto** 193 casi per anno - 12.4%	2	**Colon retto** 154 casi per anno - 13.1%	2	**Colon retto** 347 casi per anno - 12.7%
3	**Stomaco** 142 casi per anno - 9.1%	3	**Bronchi e polmoni** 118 casi per anno - 10.0%	3	**Stomaco** 241 casi per anno - 8.8%
4	**Prostata** 141 casi per anno - 9.1%	4	**Stomaco** 99 casi per anno - 8.4%	4	**Mammella** 178 casi per anno - 6.5%
5	**Fegato dotti intraepatici** 87 casi per anno - 5.6%	5	**Pancreas** 86 casi per anno - 7.3%	5	**Pancreas** 166 casi per anno - 6.1%

Primo tumore per frequenza



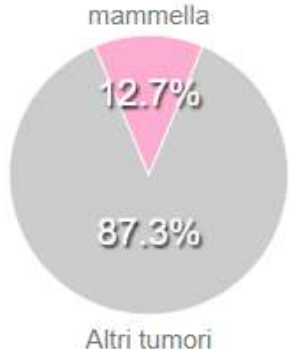
Periodo completo: 1994 - 2011 | **Ultimi 10 anni: 2002 - 2011** | Ultimi 5 anni: 2007 - 2011

Rank	Maschi	Rank	Femmine	Rank	Tutta la popolazione
1	**Prostata** 665 casi per anno - 21.3%	1	**Mammella** 691 casi per anno - 27.2%	1	**Colon retto** 860 casi per anno - 15.2%
2	**Colon retto** 483 casi per anno - 15.5%	2	**Colon retto** 377 casi per anno - 14.8%	2	**Mammella** 699 casi per anno - 12.3%
3	**Bronchi e polmoni** 426 casi per anno - 13.6%	3	**Stomaco** 148 casi per anno - 5.8%	3	**Prostata** 665 casi per anno - 11.7%
4	**Vie urinarie** 262 casi per anno - 8.4%	4	**Bronchi e polmoni** 143 casi per anno - 5.6%	4	**Bronchi e polmoni** 568 casi per anno - 10.0%
5	**Stomaco** 207 casi per anno - 6.6%	5	**Corpo dell'utero** 126 casi per anno - 5.0%	5	**Stomaco** 355 casi per anno - 6.3%

Rank	Femmine	Rank	Tutta la popolazione
1	**Mammella** 169 casi per anno - 12.7%	1	**Bronchi e polmoni** 490 casi per anno - 16.3%
2	**Colon retto** 141 casi per anno - 10.6%	2	**Colon retto** 308 casi per anno - 10.2%
3	**Bronchi e polmoni** 130 casi per anno - 9.7%	3	**Stomaco** 204 casi per anno - 6.8%
4	**Pancreas** 102 casi per anno - 7.7%	4	**Pancreas** 185 casi per anno - 6.2%
5	**Stomaco** 88 casi per anno - 6.6%	5	**Mammella** 171 casi per anno - 5.7%

844 casi nel periodo 2012-2016

In media 169 casi per anno

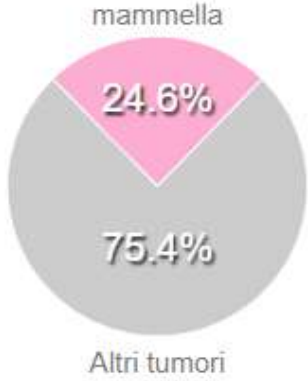


Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
29.09

Rank	Femmine	Rank	Tutta la popolazione
1	**Mammella** 791 casi per anno - 24.6%	1	**Mammella** 798 casi per anno - 11.4%
2	**Colon retto** 350 casi per anno - 10.9%	2	**Colon retto** 775 casi per anno - 11.1%
3	**Bronchi e polmoni** 176 casi per anno - 5.5%	3	**Prostata** 703 casi per anno - 10.0%
4	**Tiroide** 140 casi per anno - 4.4%	4	**Bronchi e polmoni** 607 casi per anno - 8.7%
5	**Stomaco** 136 casi per anno - 4.2%	5	**Vie urinarie** 333 casi per anno - 4.7%

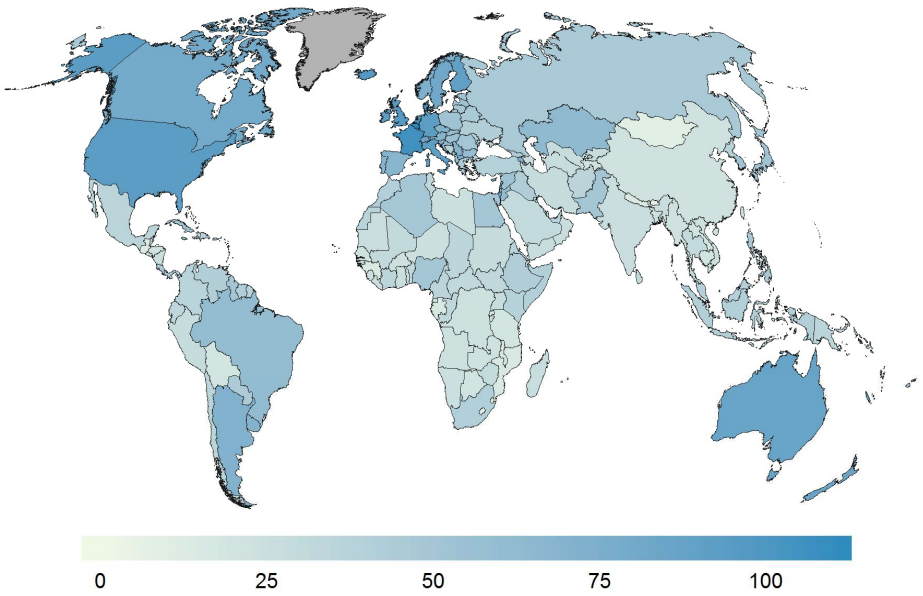
3957 casi nel periodo 2011-2015

In media 791 casi per anno



Tasso standardizzato per 100,000 abitanti, popolazione Italia 2011:
155.06

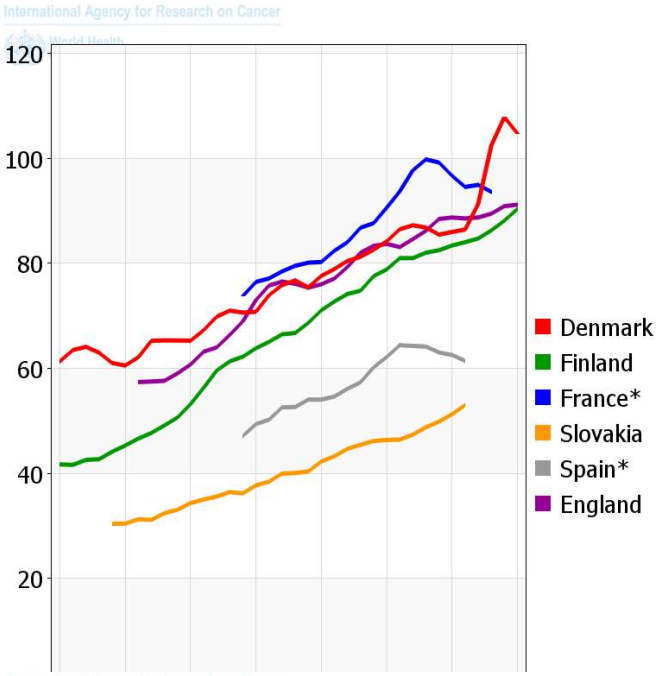
Incidenza del cancro della mammella (GLOBOCAN 2012)

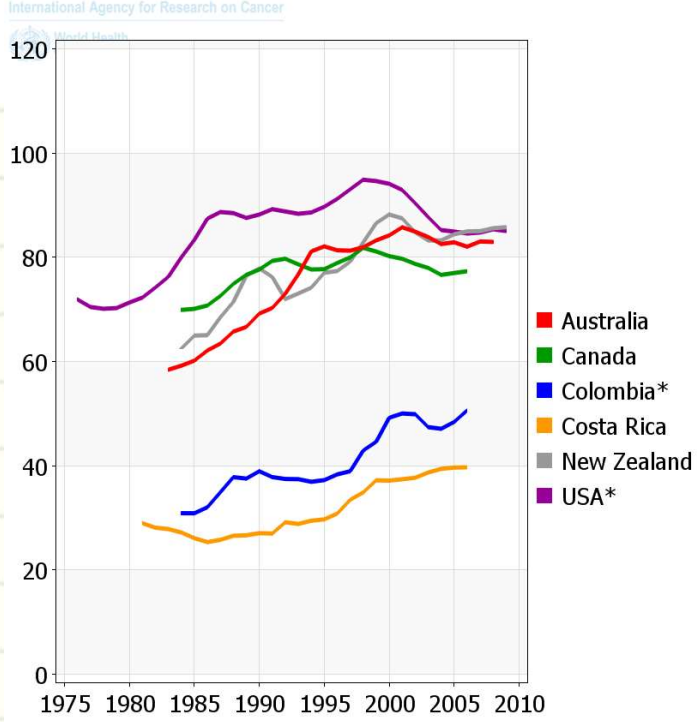


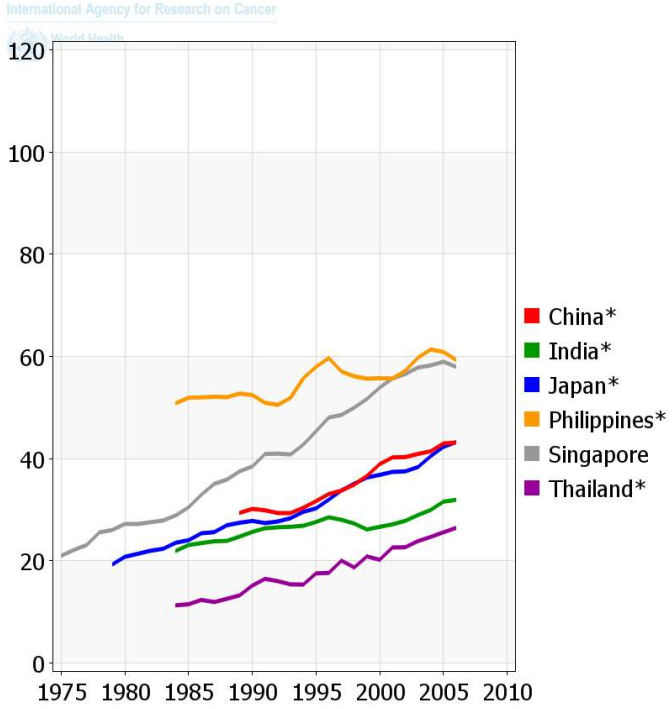
Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers).

It is the most common cancer in women both in more and less developed regions with slightly more cases in less developed (883,000 cases) than in more developed (794,000) regions

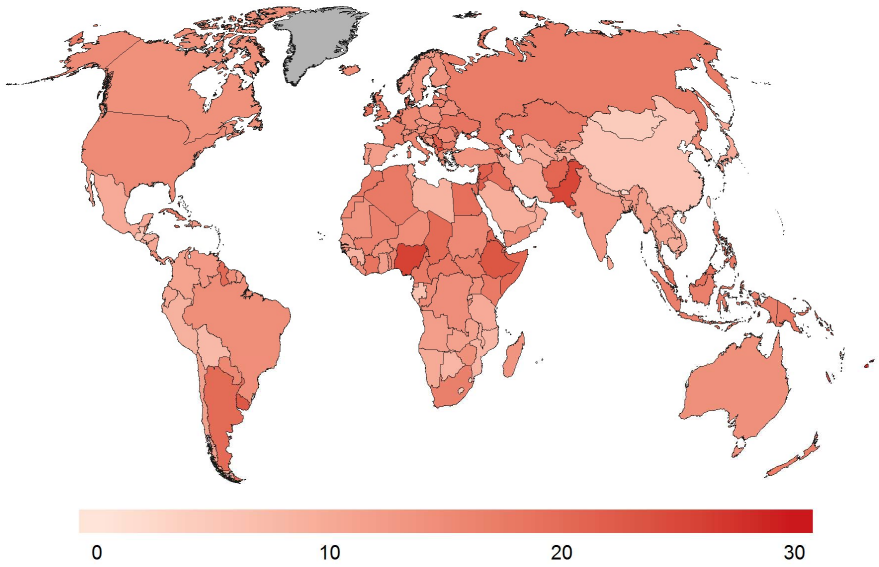
Trend di incidenza in alcuni paesi







Mortalità per cancro della mammella



Breast cancer ranks as the fifth cause of death from cancer overall (522,000 deaths)

Although breast cancer incidence remains highest in more developed countries (500,000 new cases registered in WHO European Region compared with 100,000 cases in Africa), mortality is relatively much higher in low-income countries because of late diagnosis and insufficient effective treatment.

While it is the most frequent cause of cancer death in women in less developed regions (324,000 deaths, 14.3% of total), it is now the second cause of cancer death in more developed regions (198,000 deaths, 15.4%) after lung cancer.

Incidenza in Italia (in alto) e Umbria (in basso)

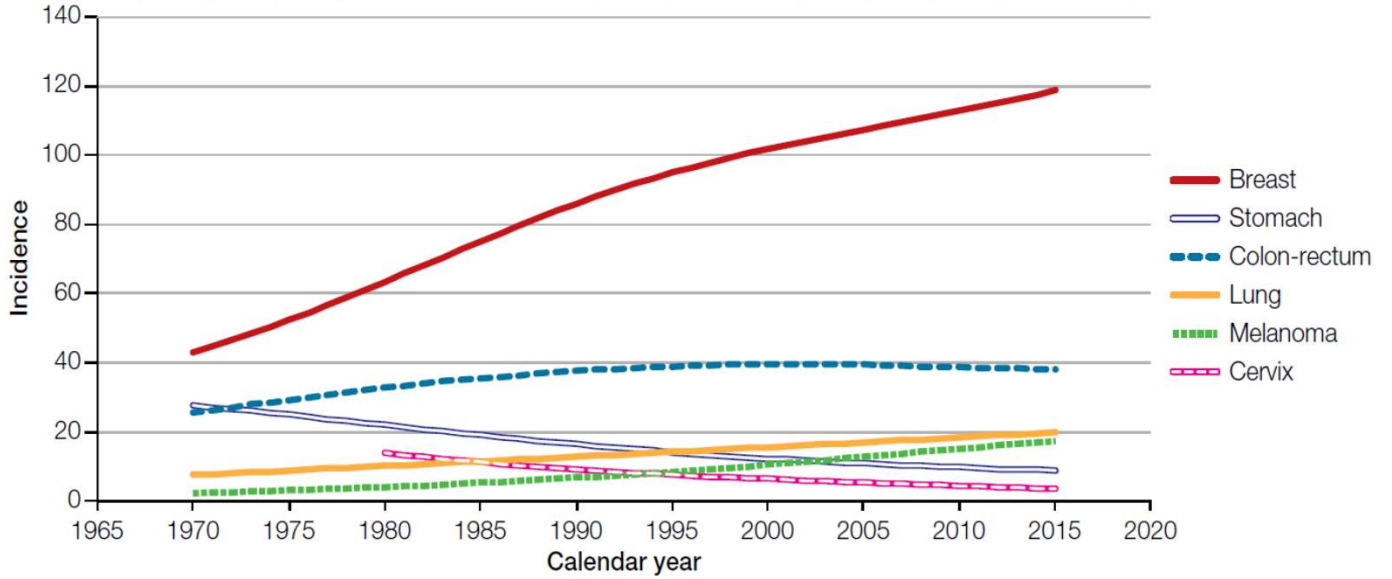


Figura 2 - Incidence estimates by cancer site in Italy in the period 1970-2015. Age-standardized rates (European population) per 100,000 person-years. Age 0-99 years, women.

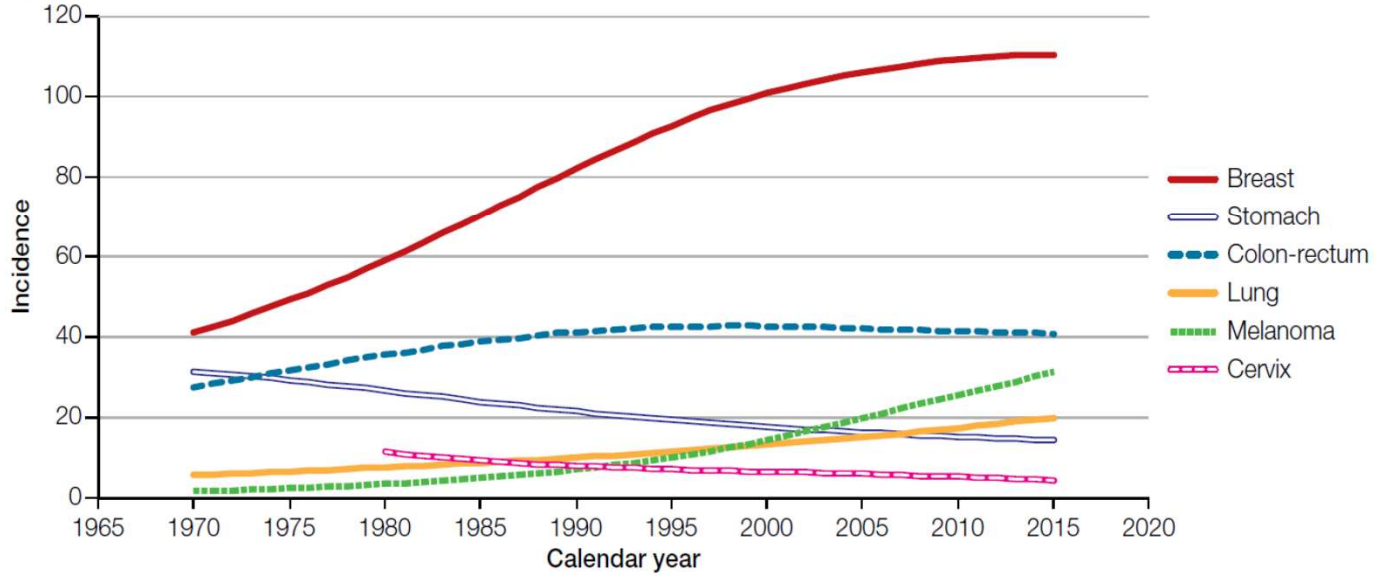


Figure 2 - Incidence estimates by cancer site in Umbria in the period 1970-2015. Age-standardized rates (European population) per 100,000 person-years. Age 0-99 years, women.

Mortalità in Italia (in alto) e Umbria (in basso)

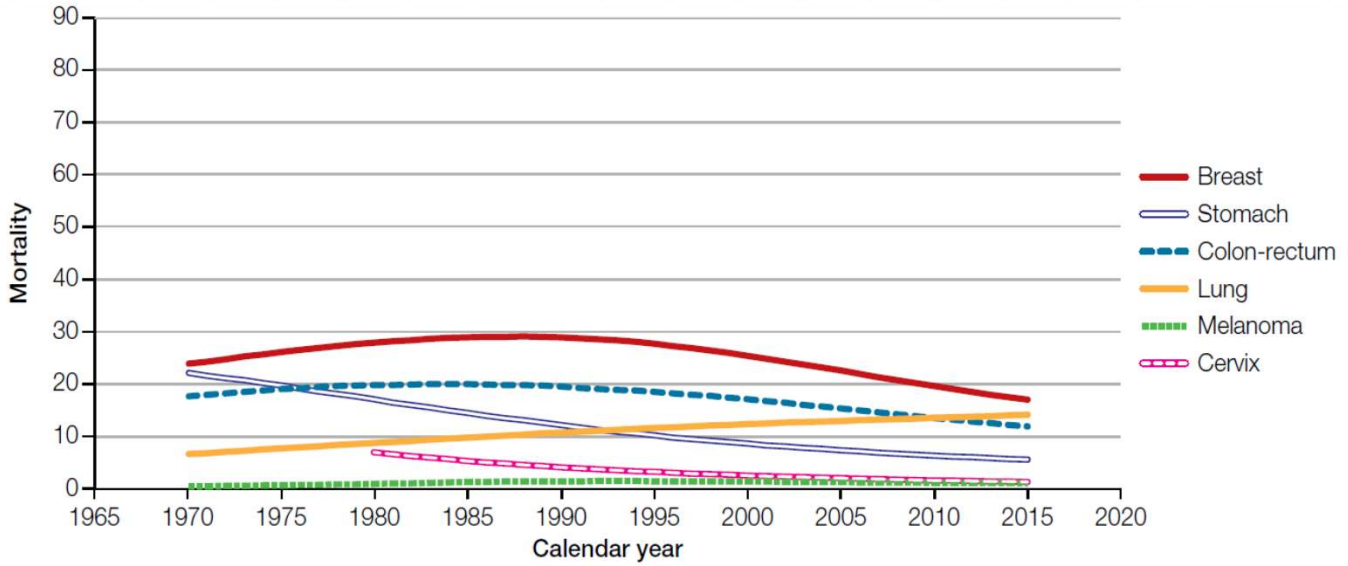


Figura 4 - Mortality estimates by cancer site in Italy in the period 1970-2015. Age-standardized rates (European population) per 100,000 person-years. Age 0-99 years, women.

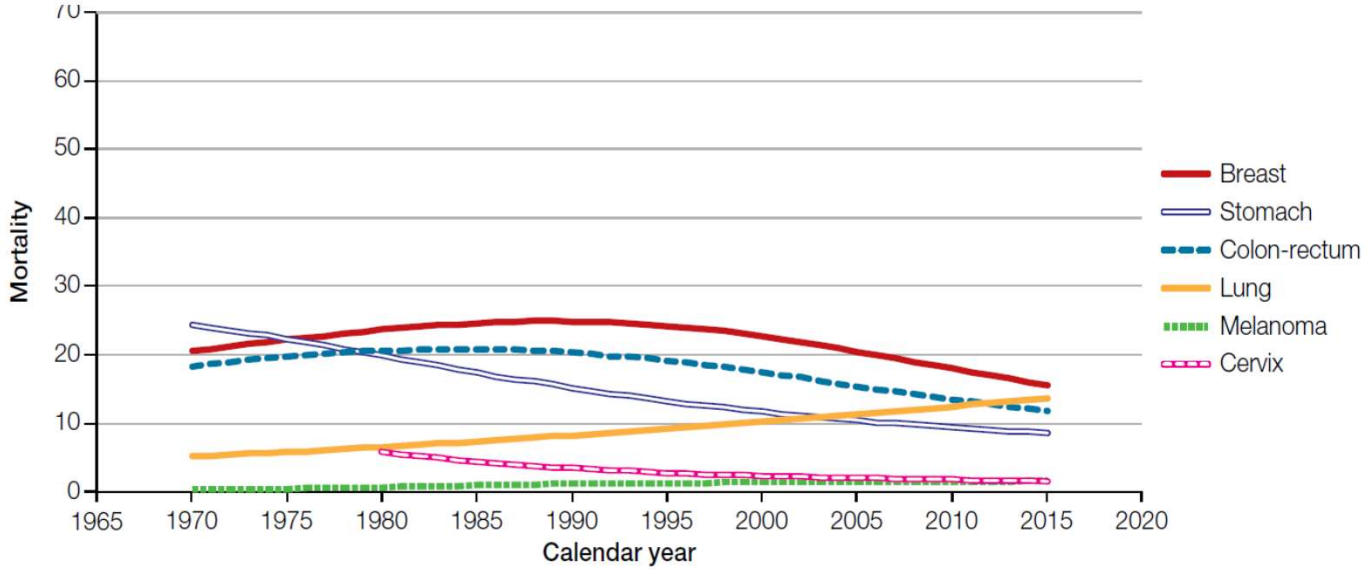


Figure 4 - Mortality estimates by cancer site in Umbria in the period 1970-2015. Age-standardized rates (European population) per 100,000 person-years. Age 0-99 years, women.

Un problema di dimensioni crescenti

- The current lifetime risk of a woman developing breast cancer in the US is estimated to be one in eight (12.3%), which is an increase compared to the one in eleven (9.09%) lifetime risk in the 1970s.
- This apparent increase is believed to result from
  - longer life expectancy,
  - increased detection through sensitive screening methods,
  - changes in reproductive patterns, and an increasing prevalence of obesity

Fattori di rischio

Global cancer patterns: causes and prevention. Vineis P, Wild C. Lancet 2014

Reproductive factors

… Increases in **breast cancer** in low-HDI countries will be largely due to changes in reproductive practices, with women choosing to have **fewer children, have their first pregnancy later in life, and breastfeed for a shorter period**.

Diet, obesity, and physical inactivity

- **Obesity is a risk factor for breast (post-menopausal)**, colorectal, endometrium, kidney, oesophageal, and pancreatic cancers.
- **Alcohol** is associated with liver, upper aerodigestive tract, **breast**, and colorectal cancers.
- **Low physical activity** is a **major risk factor** for colon, **breast**, and endometrial cancers, both indirectly through its effect on body-mass index (BMI), and directly through other, only partly understood, mechanisms

Strategie di prevenzione

- Risk factors are inherited, histopathologic or environmental, each of which is important.
- Strategies to decrease environmental risks generally focus on directly addressing the environmental factor,
- whereas genetic and histopathologic risks, which cannot so easily be altered directly, are addressed indirectly, such as through altering known drivers to breast cancer, such as estrogen and its receptor through chemoprevention, or by surgical extirpation of the organ(s) at risk.
- Mammographic breast density (MBD) also influences breast cancer risk. MBD is appears to be influenced by genetics (4), age and body mass index (5).

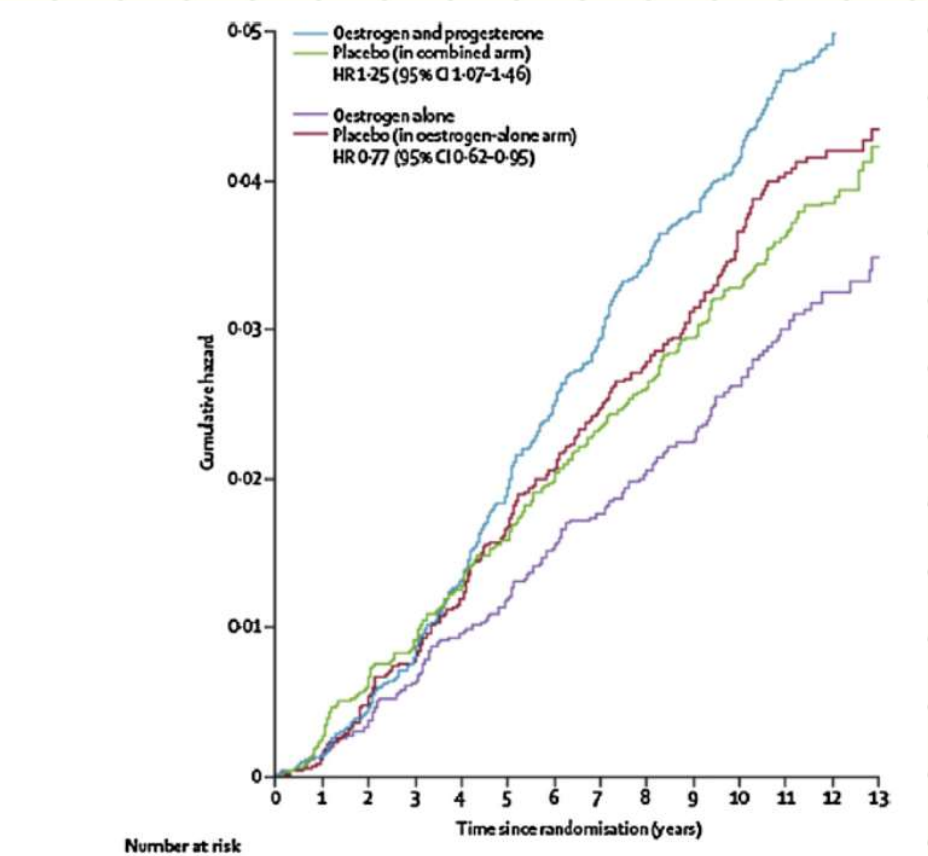
Terapia ormonale sostitutiva

The WHI started HT treatment on women aged 50-79 years in order to ascertain these effects. The study was ended early, due to findings of **increased risk of** coronary heart disease, **breast cancer**, stroke, and thromboembolic complications in women receiving estrogen plus progestin, compared to placebo.

Solo estrogeni

Anderson et al. found a 23% reduction in the incidence of invasive breast cancer with ET compared with placebo (151 cases, 0.27% per year versus 199 cases, 0.35% per year) during an overall follow-up period of nearly 12 years

Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomized placebo-controlled trial, Lancet Oncol 13 (2012) 476–486



Number at risk							
Combined arm							
Oestrogen and progesterone	8506	8329	8109	7796	7009	6189	2914
Placebo	8102	7914	7721	7466	6692	5889	2648
Oestrogen-alone arm							
Oestrogen alone	5310	5166	5007	4840	4261	3620	1696
Placebo	5429	5280	5106	4915	4301	3678	1771

Fig. 4. Breast cancer risk for E+P and ET versus placebo. Cumulative hazards, adjusted for age and ethnic group, of invasive breast cancer by allocation into the WHI E+P and ET trials.

Terapia ormonale e incidenza

- There was a sharp decrease in breast cancer incidence … in the United States, evident in white women 50 years of age and for estrogen receptor (ER) positive tumors. This has been attributed to the reduced use of hormone replacement therapy (HRT) after the July 2002 publication from the Women's Health Initiative
- Following the sharp decrease, it was reported that a decreasing trend continued into 2005
- The most recent publications observed that the decline in cancer incidence ceased and the rate stabilized from 2004 to 2008 , with ER-positive breast cancer being projected to increase

A trend analysis of breast cancer incidence rates in the United States from 2000 to 2009 shows a recent increase. Hou N1, Huo D. Breast Cancer Res Treat. 2013;138:633-41.

Chemoprevenzione

- Based on the NSABP-P1, the NNT with daily tamoxifen for more than 5 years to prevent one case of breast cancer is 48 women;
- Recently, a meta-analysis based on individual participant data from nine randomized prevention trials using tamoxifen, raloxifene, arzoxifene, and lasofoxifene was reported.57
- Overall, a 38% reduction in the incidence of breast cancer (including DCIS) was noted (HR =0.62; 95% CI: 0.56 to 0.69), with the largest reduction in the first 5 years of follow-up compared to years 5 to 10…No effect was noted on ER-negative breast cancers

- A recent meta-analysis of seven observational studies demonstrated a protective effect of metformin on breast cancer risk in postmenopausal women with diabetes (combined OR =0.83; 95% CI: 0.71 to 0.97).64

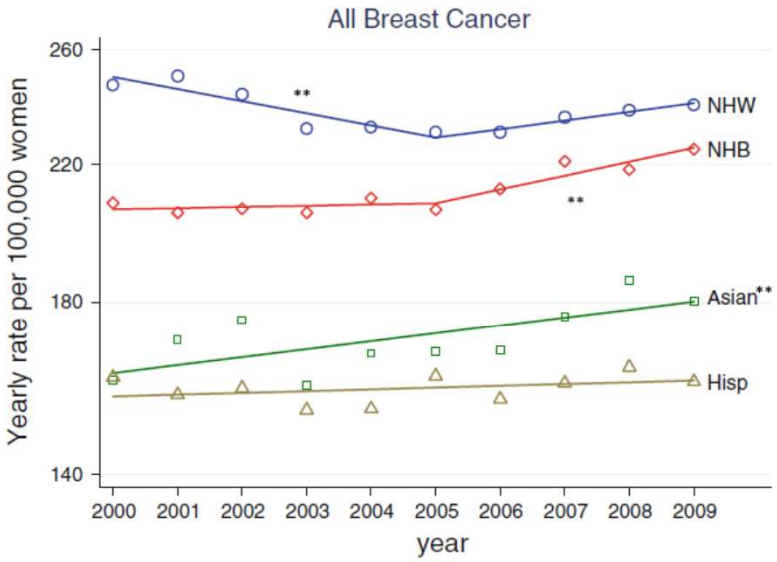
Advani et al. Current strategies for the prevention of breast cancer 2014

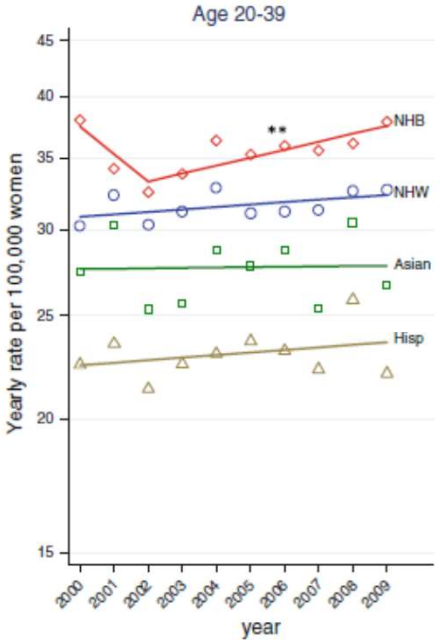
Limited use of chemoprevention

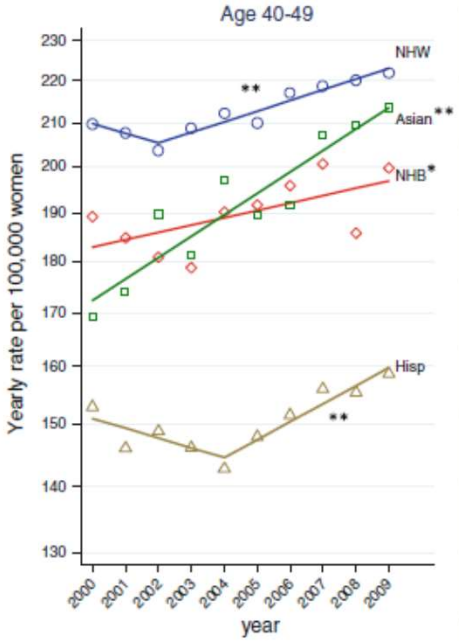
Possible explanations for the limited use of chemopreventive agents include:

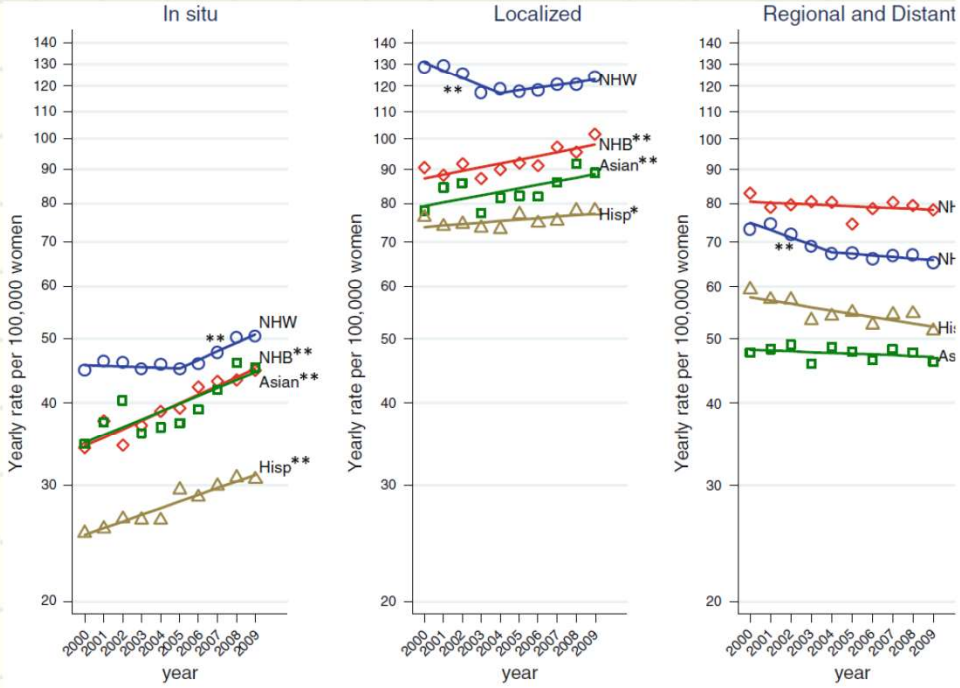
- difficulty in identifying the ideal candidates for chemoprevention strategies;
- decreased awareness among high-risk women and health care providers;
- concerns about adverse effects of the agents; and their impact on quality of life in the absence of a diagnosed cancer.

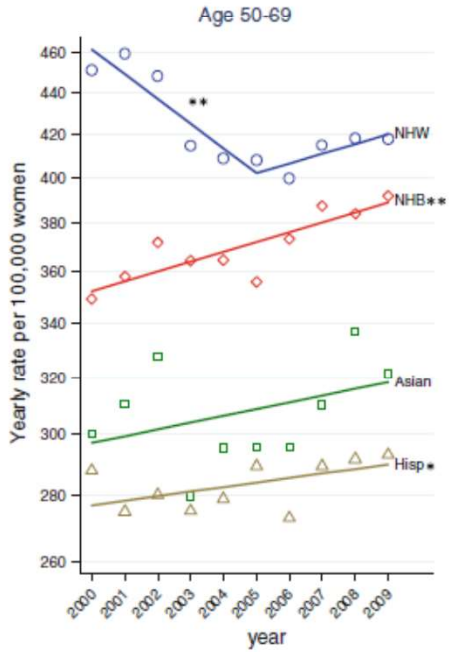
Identifying the optimal candidates for chemoprevention strategies continues to be challenging, as the existing breast cancer risk-assessment models do not incorporate all known risk factors, such as alcohol intake, use of oral contraceptive pills, density of breast tissue, and history of radiation exposure.

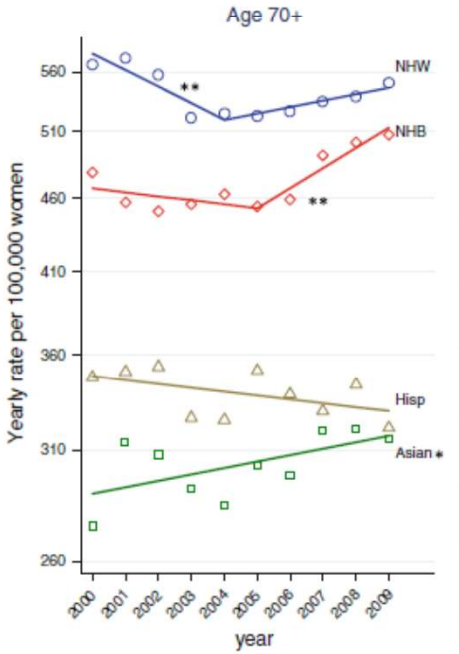

All Breast Cancer
Yearly rate per 100,000 women
260
220
180
140
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
year
NHW
NHB
Asian**
Hisp
**
**
** p<0.05


Age 20-39
Yearly rate per 100,000 women
45
40
35
30
25
20
15
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
year
NHB
NHW
Asian
Hisp
**


Age 40-49
Yearly rate per 100,000 women
230
220
210
200
190
180
170
160
150
140
130
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
year
NHW
Asian**
NHB*
Hisp
**
**


In situ
Localized
Regional and Distant
Yearly rate per 100,000 women
140
130
120
110
100
90
80
70
60
50
40
30
20
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
year
NHW
NHB**
Asian**
Hisp**
Hisp*
**
**
* 0.05 < p < 0.1; ** p < 0.05


Age 50-69
Yearly rate per 100,000 women
460
440
420
400
380
360
340
320
300
280
260
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
year
NHW
NHB**
Asian
Hisp*
**


Age 70+
Yearly rate per 100,000 women
560
510
460
410
360
310
260
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009
year
NHW
NHB
Hisp
Asian*
**
**

Programmi di screening nel carcinoma mammario

Test di screening

- Si basano sulla visualizzazione delle lesioni:
- Mammografia (digitale)
- Ecografia
- RMN
- Test di conferma: biopsia /citologia

Bersaglio del test

- Principali lesioni identificate: cancro in fase precoce

- Effetto sulla frequenza di malattia: aumento dell'incidenza
  - Transitorio in corrispondenza dell'introduzione
  - Durevole in caso di *sovra-diagnosi*

Lesioni identificate e conseguenze

- **Carcinomi infiltranti in fase precoce** (mammella, *colon retto*, melanoma, prostata)
- **Carcinomi in situ** – lesioni pre-maligne (cervice uterina, *colon retto*, mammella)

- Effetto della individuazione di carcinomi in fase precoce è l'aumento della sopravvivenza

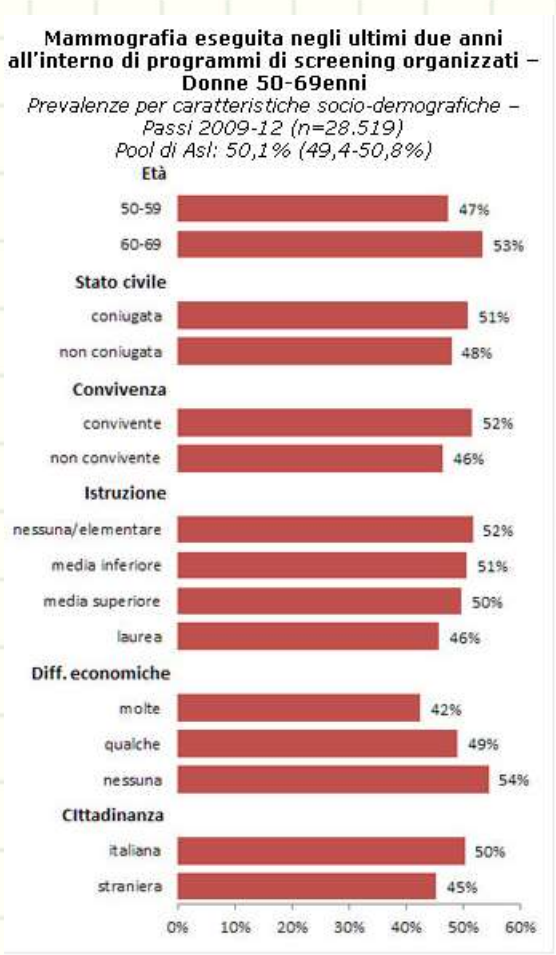
- Effetto della individuazione di lesioni premaligne evolutive è la riduzione della incidenza

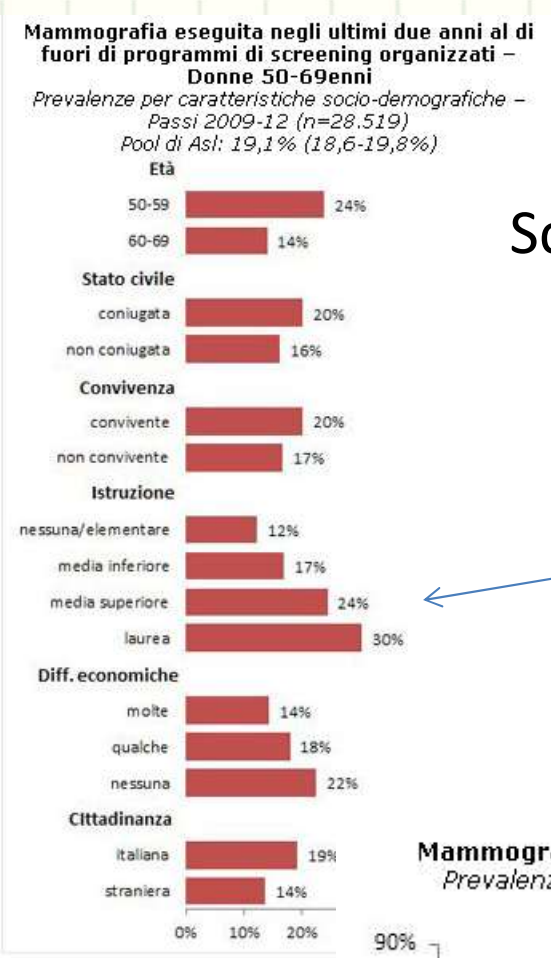
Strategia di screening

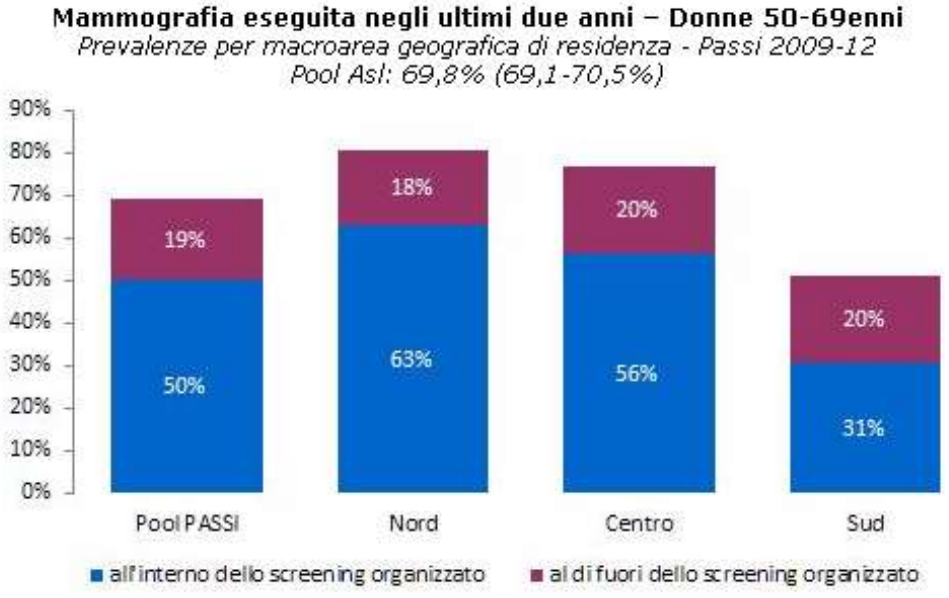
- **Organizzato**:
- Popolazione bersaglio (prevalentemente 50-69 anni)
- **Opportunistico** (non ha limiti definiti di età)

- **Misto**
- presenza di screening opportunistico dove è attivo uno screening organizzato

Screening mammografico dati studio PASSI 2012







Lo screening di popolazione

Table 6.1 . Defining criteria for organized screenings according to Hakama and colleagues

- a. The target population has been identified; +
- b. individual people are identifiable; +
- c. mechanisms are implemented to guarantee high coverage and attendance (e.g., a personal letter of invitation); +
- d. there are adequate field facilities for performing the screening tests; +
- e. there is a defined quality control program concerning how the tests are performed and interpreted; +
- f. adequate facilities exist for diagnosis and for the appropriate treatment of confirmed abnormalities; +
- g. **there is a carefully designed and agreed upon referral system, an agreed link between the participant, the screening center, and the clinical facility for diagnosis of an abnormal screening test, for management of any abnormalities found, and for providing information about normal screening tests**; and
- h. **evaluation and monitoring of the total program is organized in terms of incidence and mortality rates among those attending, among those not attending, at the level of the total target population. Quality control of the epidemiologic data should be established**.

Hakama M, Chamberlain J, Day NE, Miller AB, Prorok PC (1985). Evaluation of screening programmes for gynaecological cancer. Br J Cancer ***52,669 – 673.***

Certezza

- Lo screening mammografico è attualmente molto diffuso
- In Europa, Italia inclusa, è frequente la strategia di screening organizzato (programmi di screening)
  - Popolazione bersaglio: donne 50-69 anni
- Coesiste screening opportunistico nelle fasce d'età <50 e >=70 (strategia mista) ma anche nella fascia screening

Indagine PASSI 2010-12

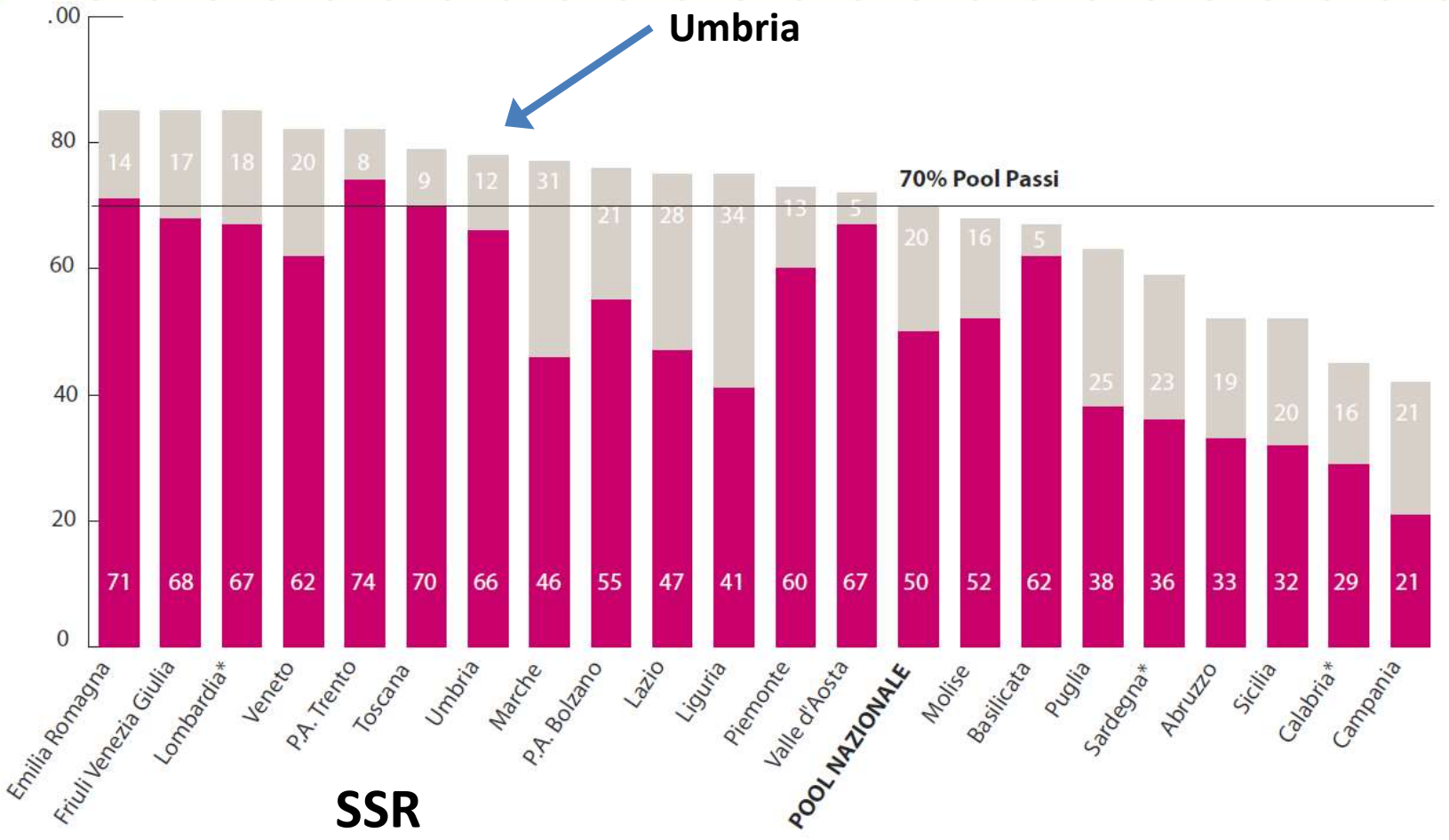


Figura 3. Mammografia eseguita negli ultimi 2 anni (%) donne 50-69enni. Passi 2010-12 (n. 19.538)

Controversie

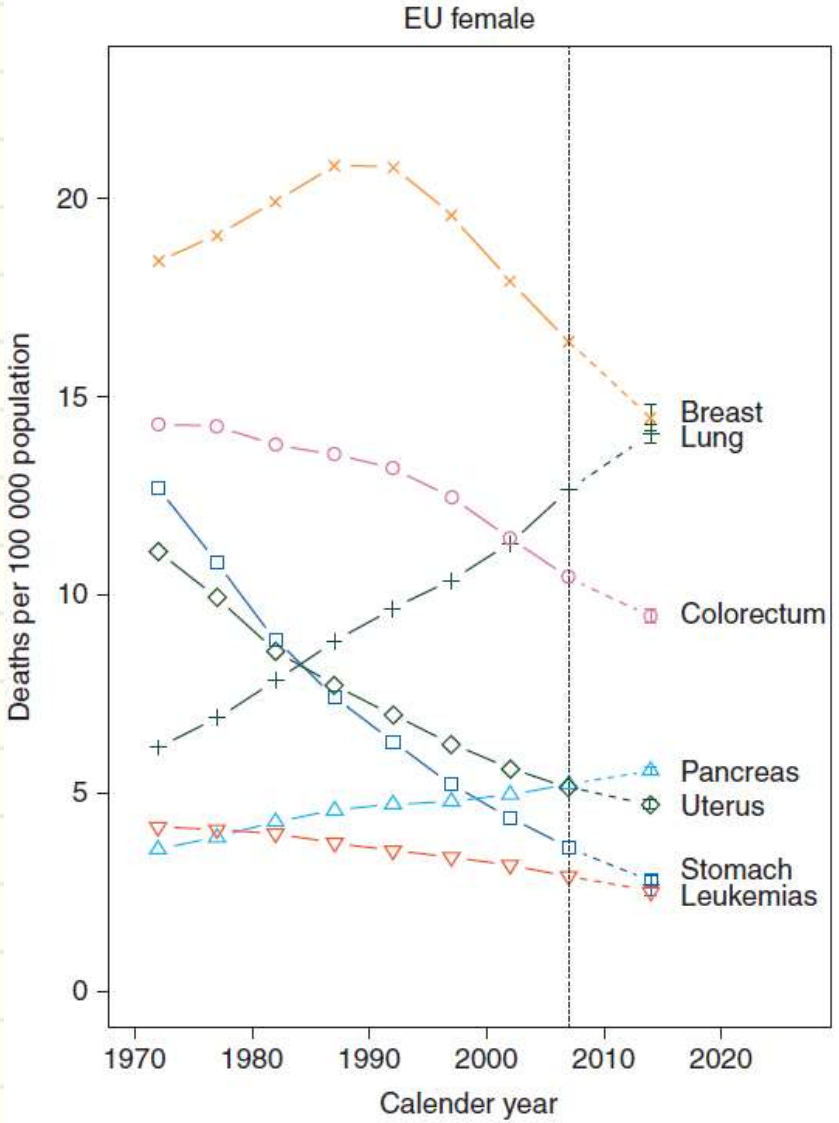
- Lo screening è efficace (riduce la mortalità)?
  - Lo screening mammografico è mai stato efficace?
  - Lo screening mammografico è attualmente efficace?
- Lo screening è responsabile di sovradiagnosi?
- [*Il bilancio tra danni e benefici giustifica il mantenimento di costosi programmi di screening?*]

Efficacia

Relative mortality benefit

- The purpose of screening is to advance the time of diagnosis so that prognosis can be improved by earlier intervention.
- A consequence of earlier diagnosis is that it increases the apparent incidence of breast cancer in a screened population and extends the average time from diagnosis to death, even if screening were to confer no benefit.
- **The appropriate measure of benefit, therefore, is reduction in mortality from breast cancer** in women offered screening compared with women not offered screening.
- In the panel's judgement, the **best evidence** for the relative benefit of screening on mortality reduction **comes from 11 randomised controlled trials (RCTs)** of breast screening

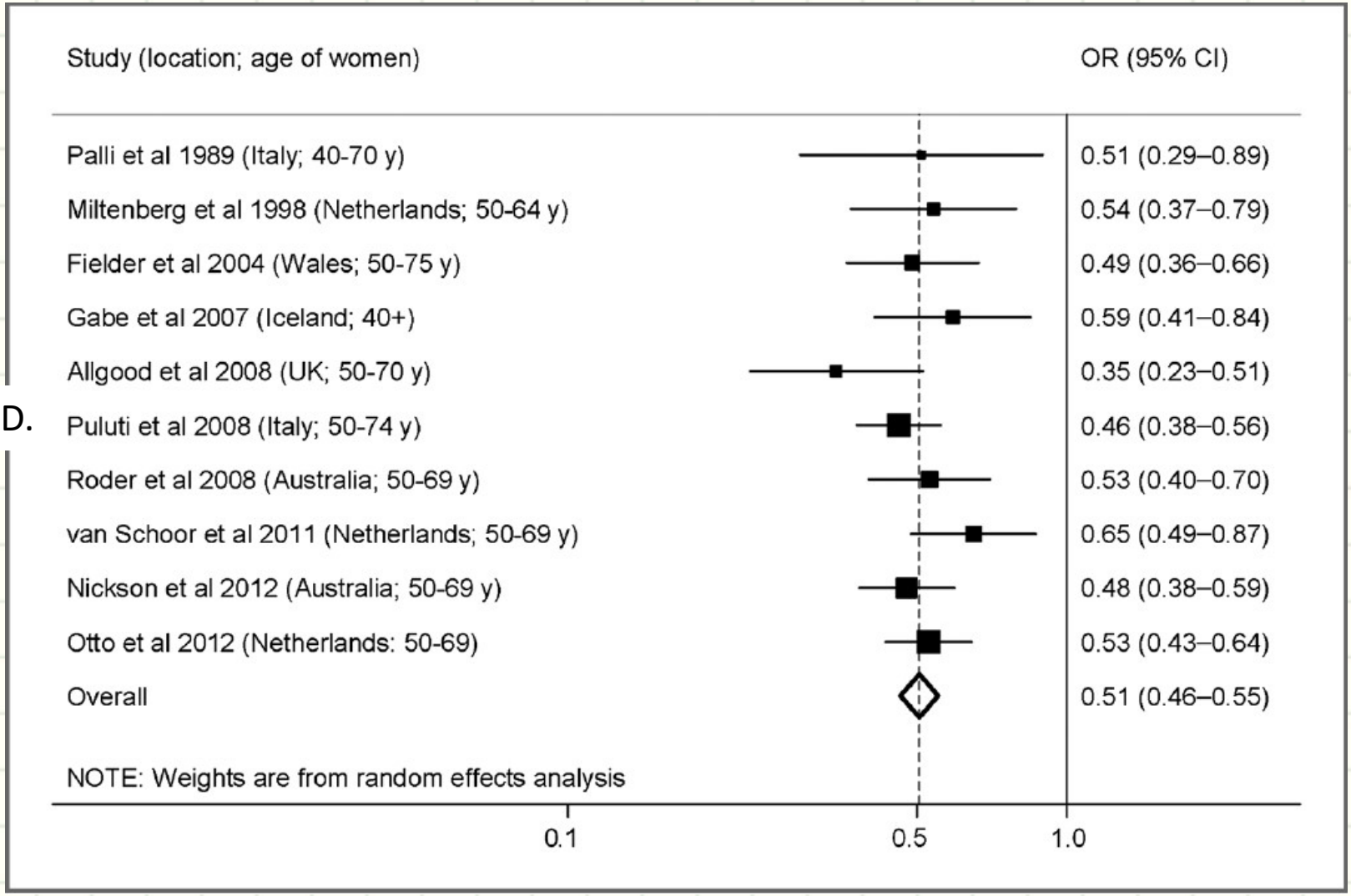
- Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. **The benefits and harms of breast cancer screening: an independent review**. *Br J Cancer*. 2013;108:2205-40



"…ecological studies comparing **areas or periods when screening programmes were and were not in place** … the Panel did **not consider these studies to be helpful** in estimation of the eff ect of screening on mortality, both because of the changes over time in the use of more effective treatments and because of the difficulty in exclusion of imbalances in other factors that could affect breast cancer mortality"
Marmot MG *BJC* 2013

Riduzione della mortalità per cancro della mammella in Europa. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2014. Ann Oncol. 2014 Apr 23

Nickson C, Mason KE, English DR, Kavanagh AM. Mammographic screening and breast cancer mortality: a case-control study and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012 ;21:1479-88.

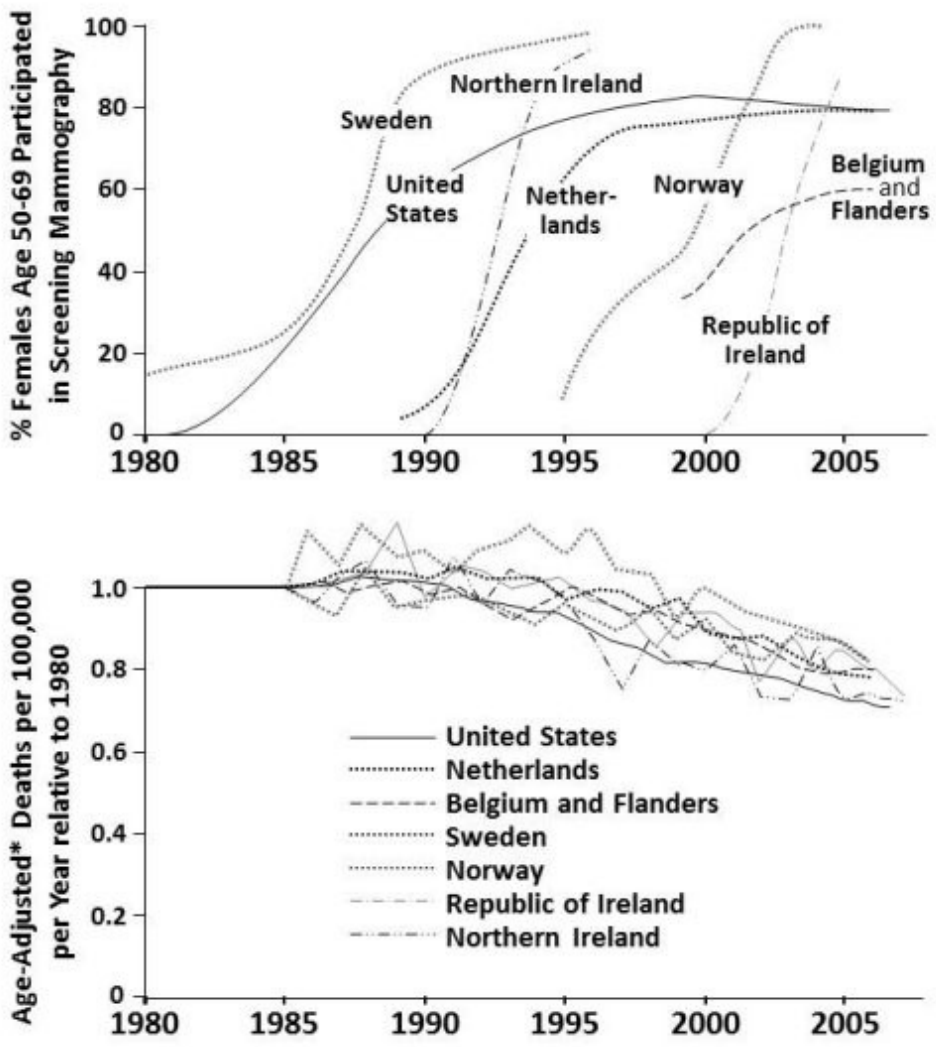


Puliti D.

Contribution of screening to decreased breast cancer mortality

- It is widely agreed that **screening alone cannot be the major factor responsible for the decrease in breast cancer mortality** over the last 20 years.
- **Improvements in treatment and service delivery** are likely to have made the largest contribution to decreased mortality (Berry et al, 2005).

The benefits and harms of breast cancer screening: an independent review. Independent UK Panel on Breast Cancer Screening. *Lancet. 2012;380:1778-86*



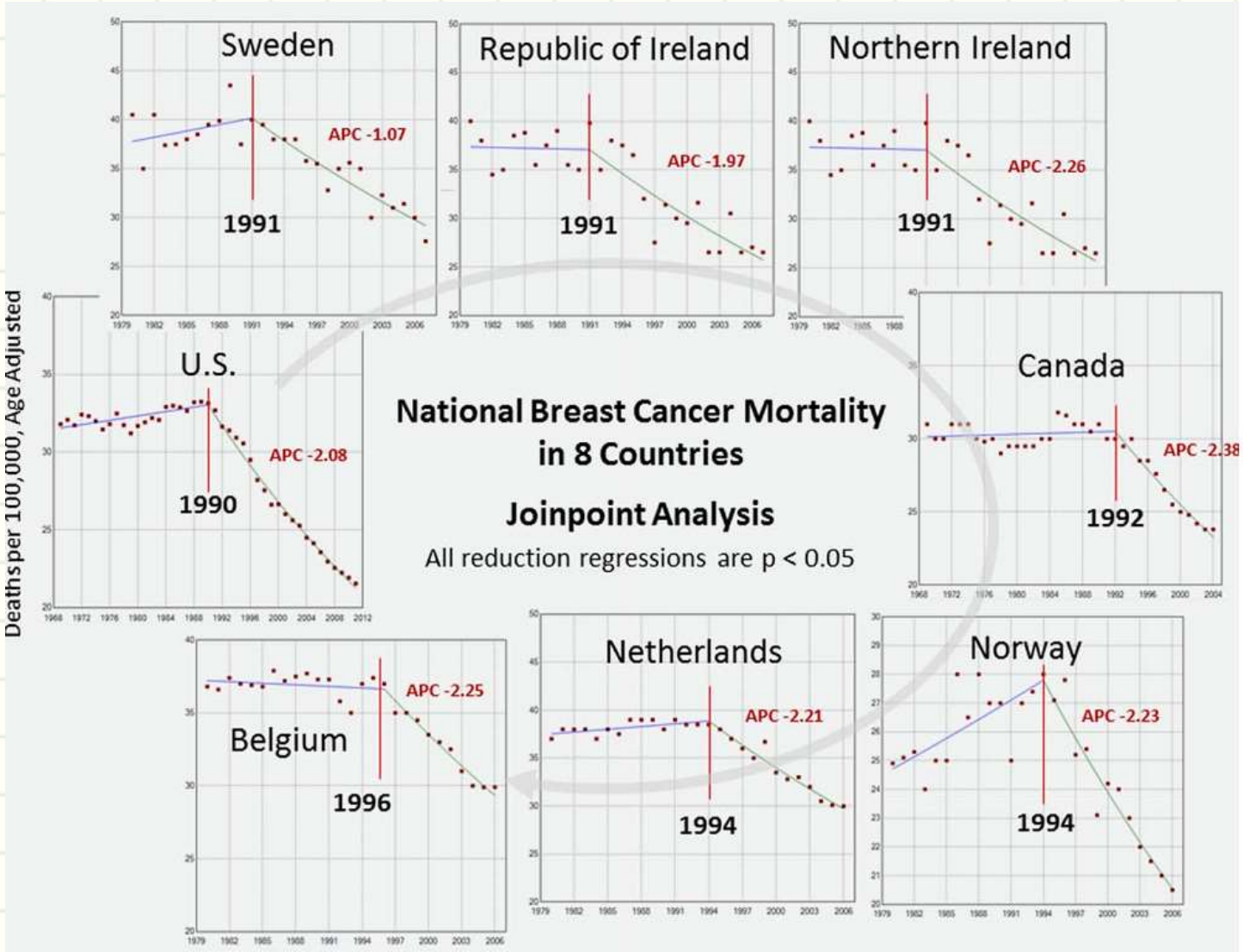
The additional data from the U.S. and the composite analysis lends further support to conclusion that **treatment and not screening has been the primary reason for mortality reduction**.

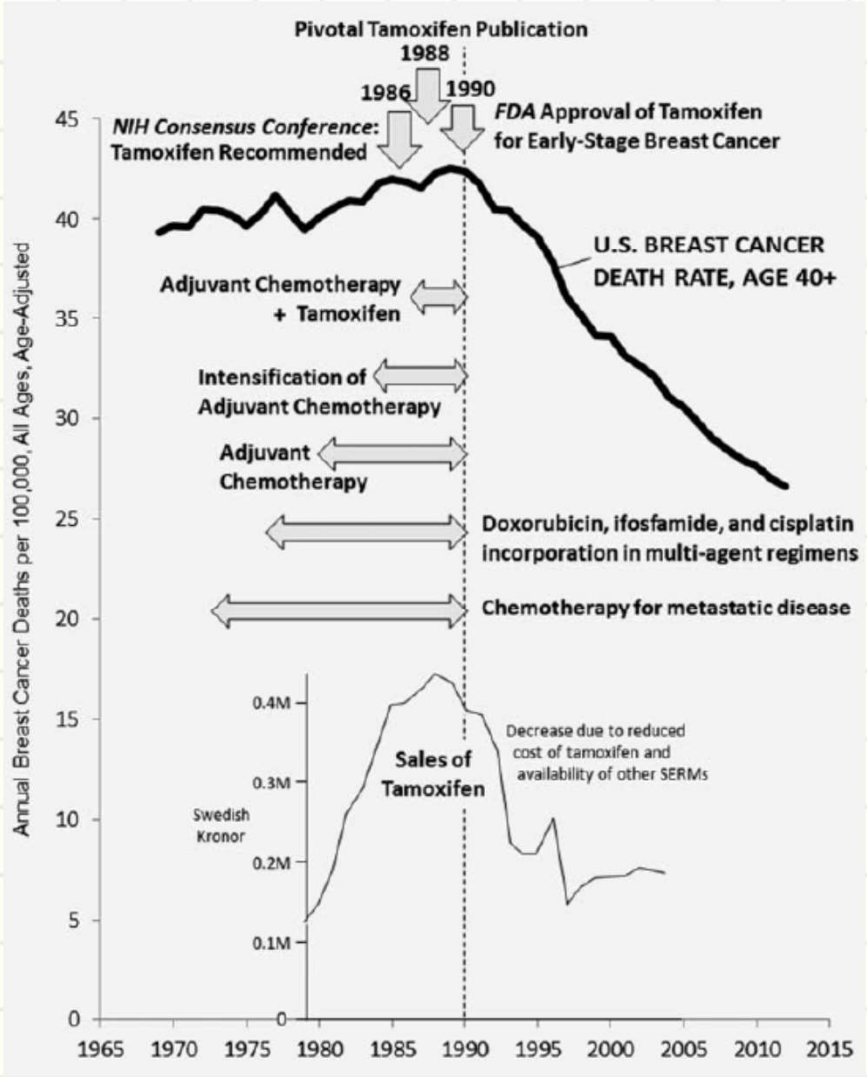
Figure 1: Percent of country's females participating in screening mammography (upper panel) and change in national breast cancer mortality rate relative to the country's mean rate during 1980-1985(lower panel).

U.S. Breast Cancer Mortality Data Consistent with European Report on Lack of Impact of Screening Mammography . Bleyer A http://www.bmj.com/content/343/bmj.d4411/reply#bmj_el_268797

Impact of screening mammography on breast cancer mortality

Archie Bleyer, Cornelia Baines and Anthony B. Miller. Int. J. Cancer: 138, 2003–2012





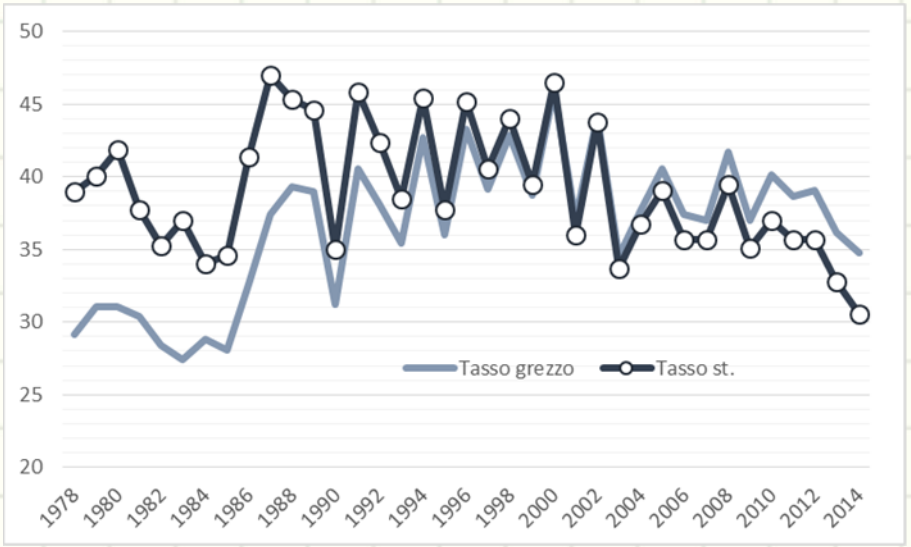


Figure 6. Therapy advances prior to the onset of the reduction in breast cancer mortality rate, United States, age 40+. The advances shown represent alternative explanations to screening mammography for the onset of breast cancer mortality reduction.

UK Panel on Breast Cancer Screening. Lancet. 2012	Overall RR (95% CI)
This review	
13-year follow-up in trials reported in the Cochrane Review[5] random-effects meta-analysis	0·80 (0·73–0·89)
Cochrane review[5]	
Fixed-effect meta-analysis of the above trials	0·81 (0·74–0·87)
As above, but excluding women <50 years	0·77 (0·69–0·86)
Trials considered adequately randomised (Canada, Malmö, and UK Age trial) had RR 0·90 (95% CI 0·79–1·02); trials deemed suboptimally randomised gave RR 0·75 (0·67–0·83). As a compromise between these two estimates, the authors concluded that an RR of 0·85 was plausible	0·85
US Task Force[9]	
RR 0·86 (95% CI 0·75–0·99) for women aged 50–59 years, and RR 0·68 (0·54– 0·87) for those aged 60–69 years. These estimates have an inverse-variance weighted average RR of 0·81	0·81
Canadian Task Force[4]	
Routinely screening for breast cancer with mammography every 2–3 years for women aged 50–69 years was rated as a weak recommendation based on moderate-quality evidence according to GRADE criteria[11]	0·79 (0·68–0·90)
Duffy et al, 2012[10]	
Review of all trials and age groups	0·79 (0·73–0·86)

RR=relative risk.

Table 2: **Estimates of RR in a comparison of invited women versus control women in the trials of breast cancer screening**

≈20%

Three types of uncertainties

Three types of uncertainties surround this estimate of 20% reduction in breast cancer mortality.

- The first is statistical: the **95% confidence interval** (CI) around the relative risk (RR) reduction of 20% was **11–27%**.
- The second is **bias**: there are a number of potential sources of distortion in the trials that have been widely discussed in the literature ranging from **suboptimal randomisation** to **problems in adjudicating cause of death**.
- *The third is the relevance of these **old trials** to the current screening programmes*

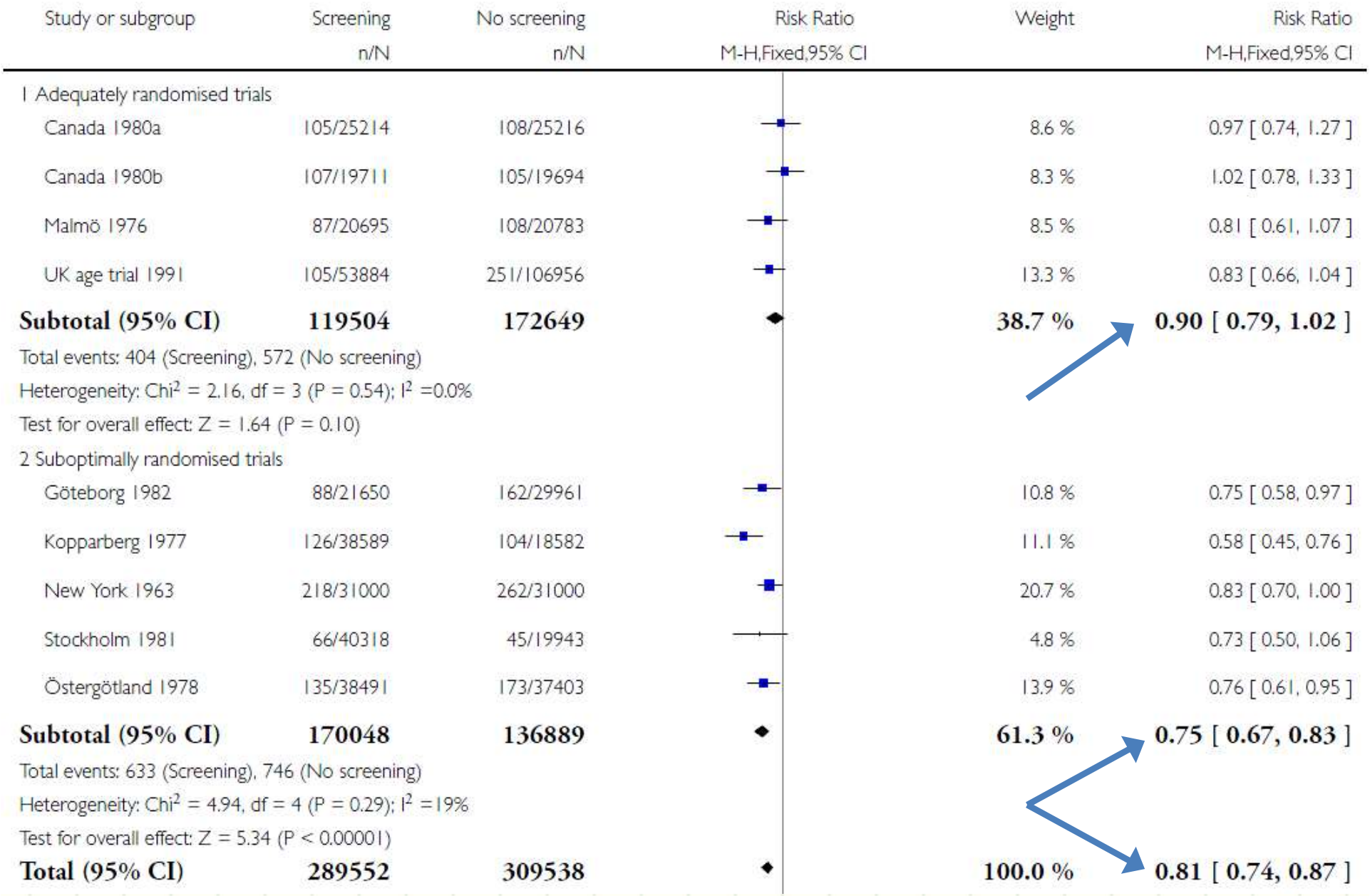
Marmot MG *BJC* 2013

Qualità dei trial e inclusione nella meta-analisi

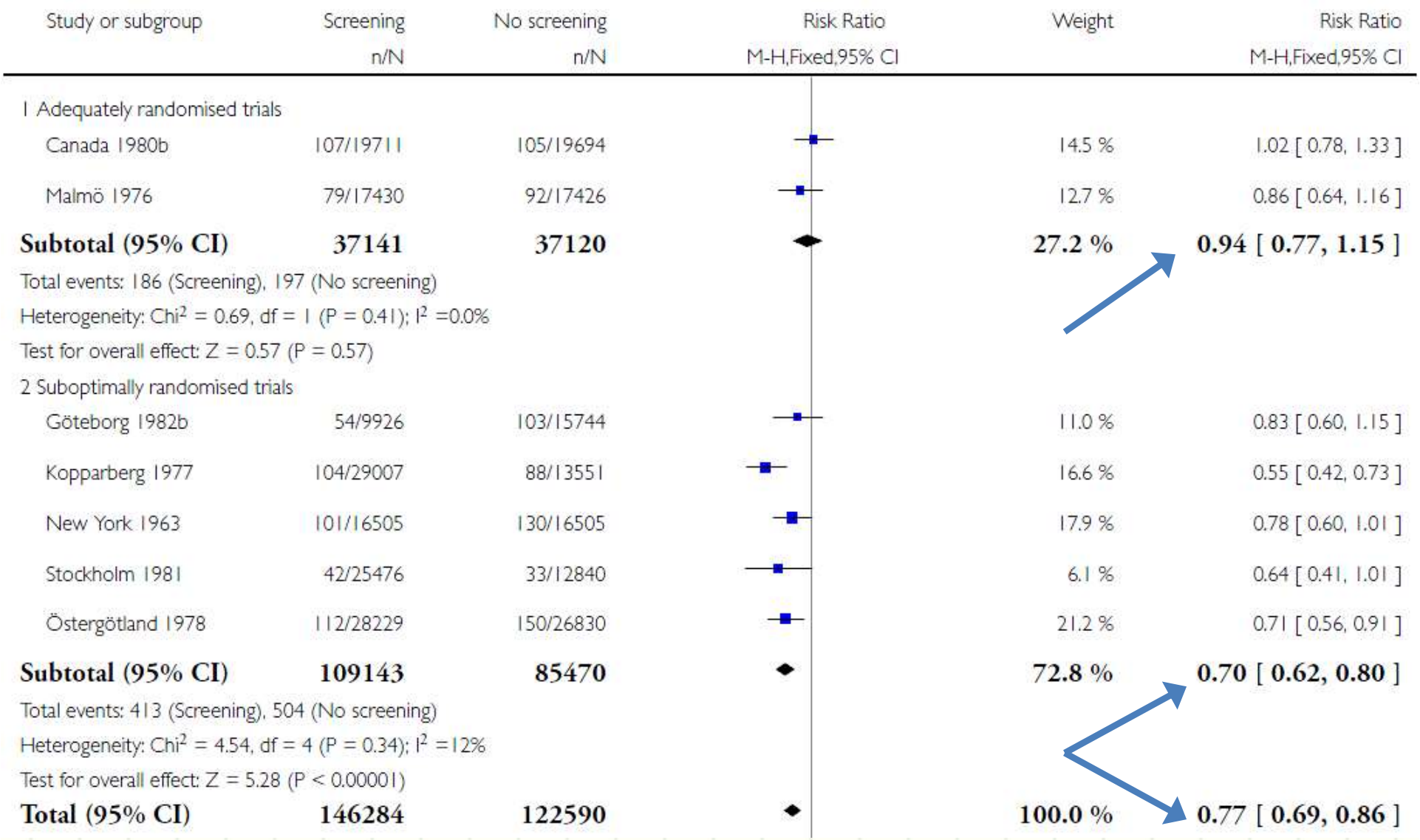
Randomised controlled trials potentially provide the most reliable information about the effects of breast screening

- We assessed whether the randomisation was adequate and led to comparable groups following standard criteria as closely as possible (Higgins 2008).
- We divided the trials into those with adequate randomisation and those with suboptimal randomisation

Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography (Review). *The Cochrane Library* 2013; 6

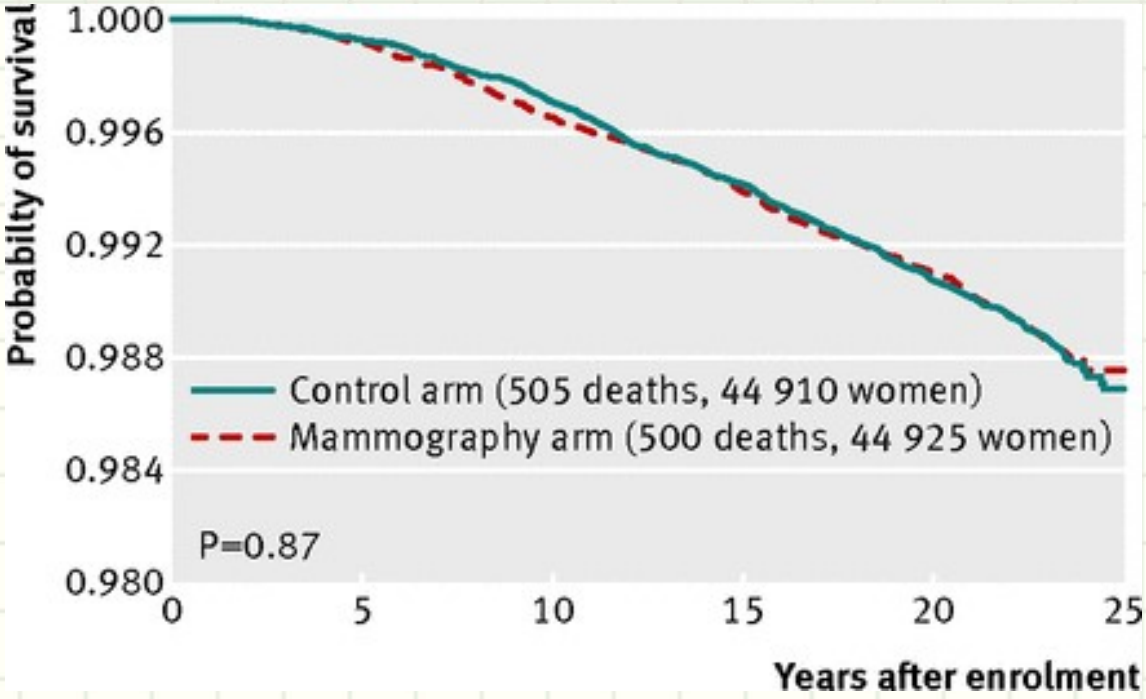


Screening with mammography versus no screening,
Deaths ascribed to breast cancer, 13 years follow up.



Screening versus no screening, Deaths ascribed to breast cancer, 13 years follow up, women at least 50 years of age.

Miller A. et al. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial BMJ 2014; 348



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. Overall, 22% (106/484) of screen detected invasive breast cancers were over-diagnosed, representing one over-diagnosed breast cancer for every 424 women who received mammography screening in the trial

Screening per classe d'età

1/0,000525≅1904

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.

- Maggiore efficacia nella classe d'età 60-69
- Insufficiente evidenza nelle donne ≥70 anni *(negli US lo screening è diffuso anche >80 anni)*

- *Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. JAMA. 2014;311:1327-35*
- **ARR =* Absolute Risk Reduction NEITHER adjusted risk ratio NOR "We also report absolute risk ratios calculated by inverting the NNI" ☹

Variabili stime del "Number needed to invite/screen" (per prevenire 1 decesso)

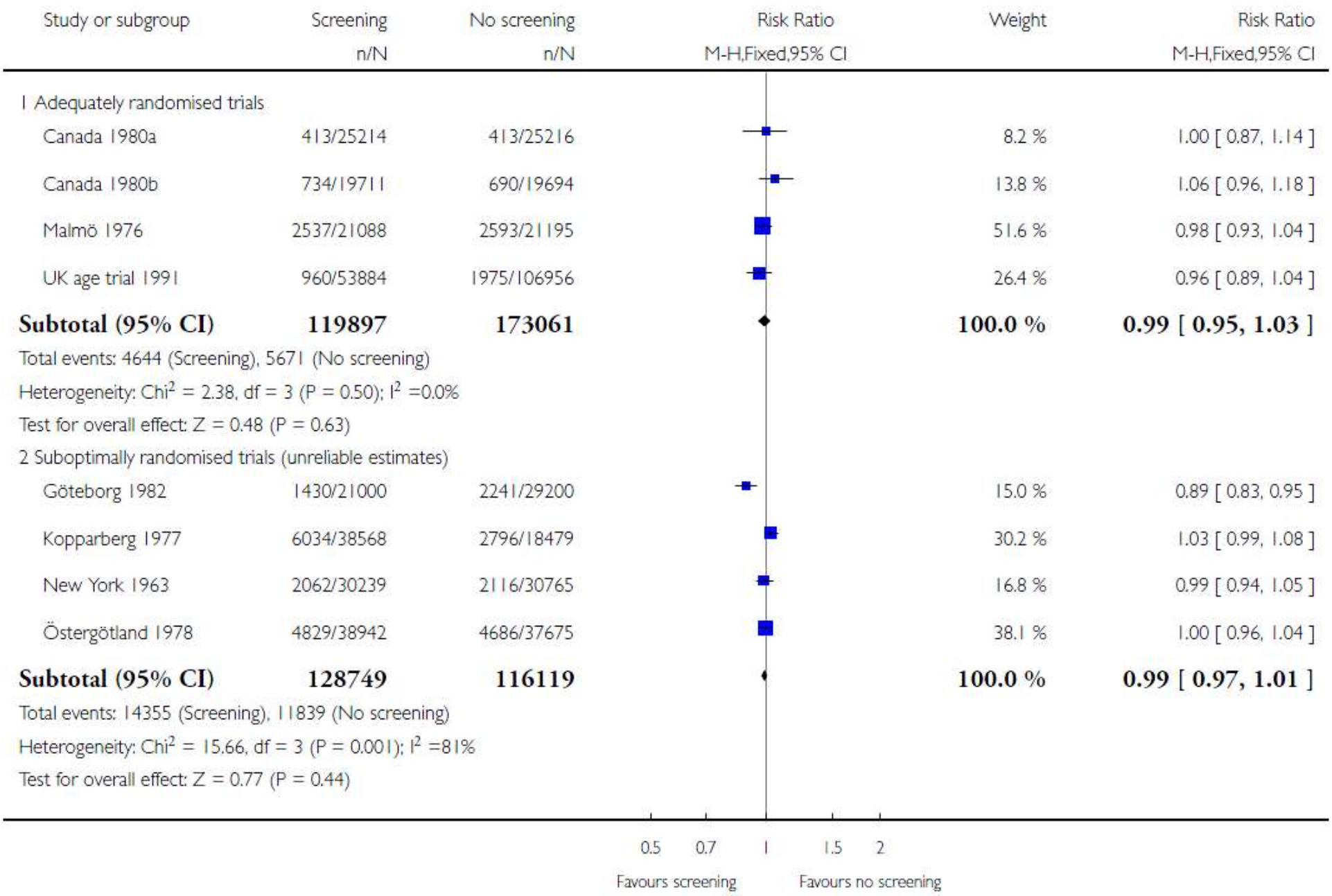
	Description	Number of women
This review	Based on an RR reduction of 20% for women aged 55–79 years in the UK	235 women invited, 180 women screened
Cochrane review[5]	Absolute risk reduction based on the 13-year follow-up in the trials considered adequately randomised	2000 women invited
US Task Force[9]	Based on 7 years of screening and 13 years of follow-up	1339 women invited aged 50–59 years, and 377 invited aged 60–69 years
Canadian Task Force[4]	Women aged 50–69 years screened every 2–3 years for about 11 years	720 women screened
Duffy et al, 2010[12]	Based on 22-year follow-up of women aged 50–69 years in the Swedish Two-County trial, assuming that the absolute risk reduction for the 7 years of screening can be multiplied up to reflect 20 years in the UK screening programmes	113 women screened
Beral et al, 2011[13]	Women aged 50–70 years regularly screened for 10 years, based on summary of published evidence	400 women screened

RR=relative risk.

Table 3: Absolute risk reduction, expressed as number of women who need to be invited or screened to prevent one breast cancer death, in the trials of breast cancer screening

Mortalità per tutte le cause

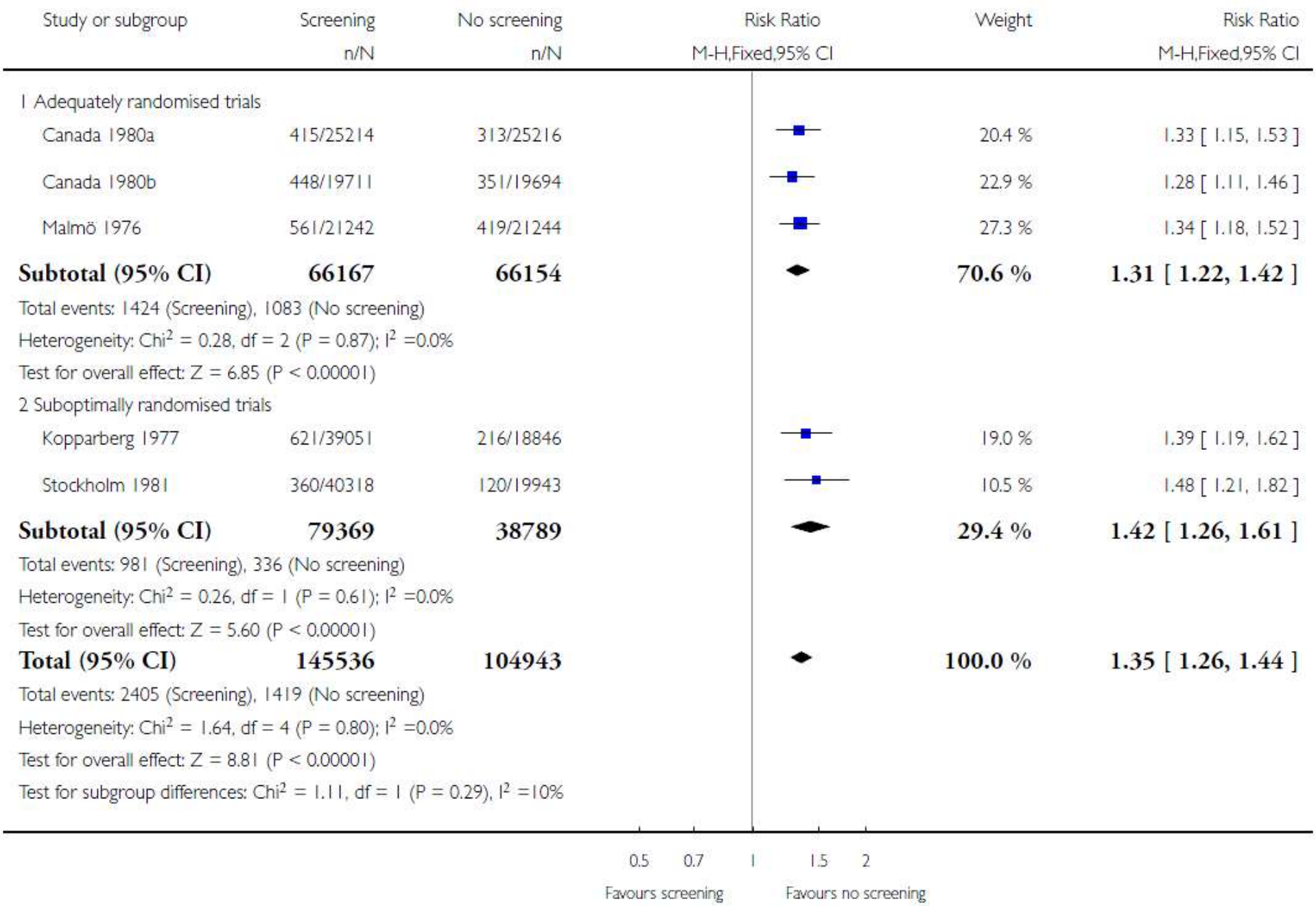
- Lo screening non modifica la mortalità complessiva



Overall mortality, 13 years follow up

Screening e trattamento

- La coorte sottoposta a screening è esposta ad un significativo aumento del rischio di intervento chirurgico

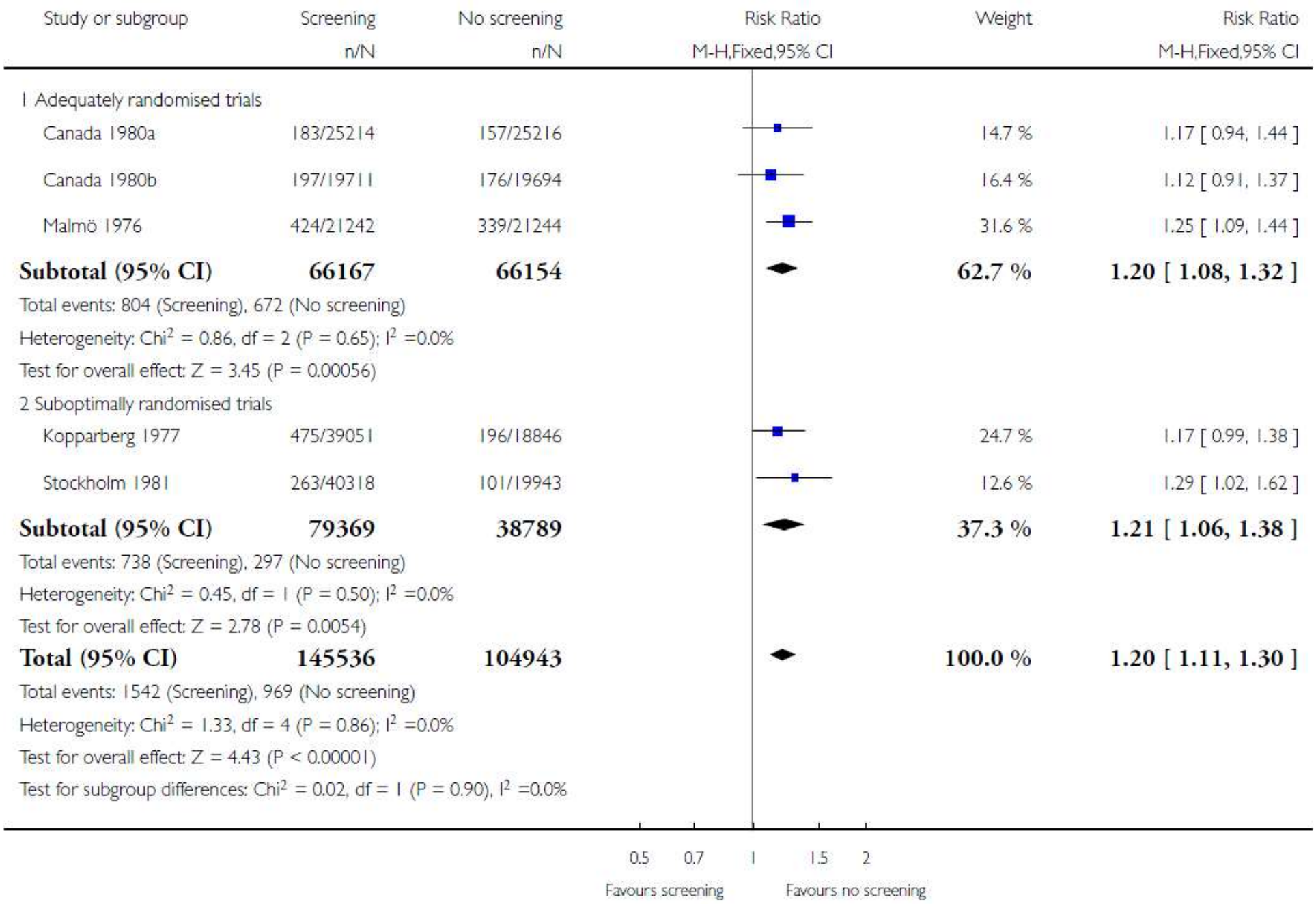


Number of mastectomies and lumpectomies

Screening e intensità di trattamento

Se il principale beneficio dello screening è rappresentato dalla guarigione (riduzione della mortalità),

- un beneficio secondario dovrebbe essere rappresentato dalla **minore intensità di cura** necessaria per trattare la malattia **in fase precoce**.
- Nonostante l'anticipazione diagnostica, **lo screening mammografico è associato ad un aumento del rischio** di ricevere trattamenti come la **mastectomia**



Screening with mammography versus no screening, number of mastectomies

Spiegazione

- Maggiore aggressività verso i casi diagnosticati allo screening (modalità di presa in carico)
- Sovra-diagnosi associata a sovra-trattamento

- La sovra-diagnosi è la diagnosi allo screening di una lesione che non avrebbe dato luogo a malattia clinica e quindi non sarebbe stata individuata nel corso della vita

Stime sovra-diagnosi

Trial:The frequency of overdiagnosis was of the order of 11% from a population perspective, and about 19% from the perspective of a woman invited to screening

Studi osservazionali: vary across the range of 0–36% of invasive breast cancers diagnosed during the screening period

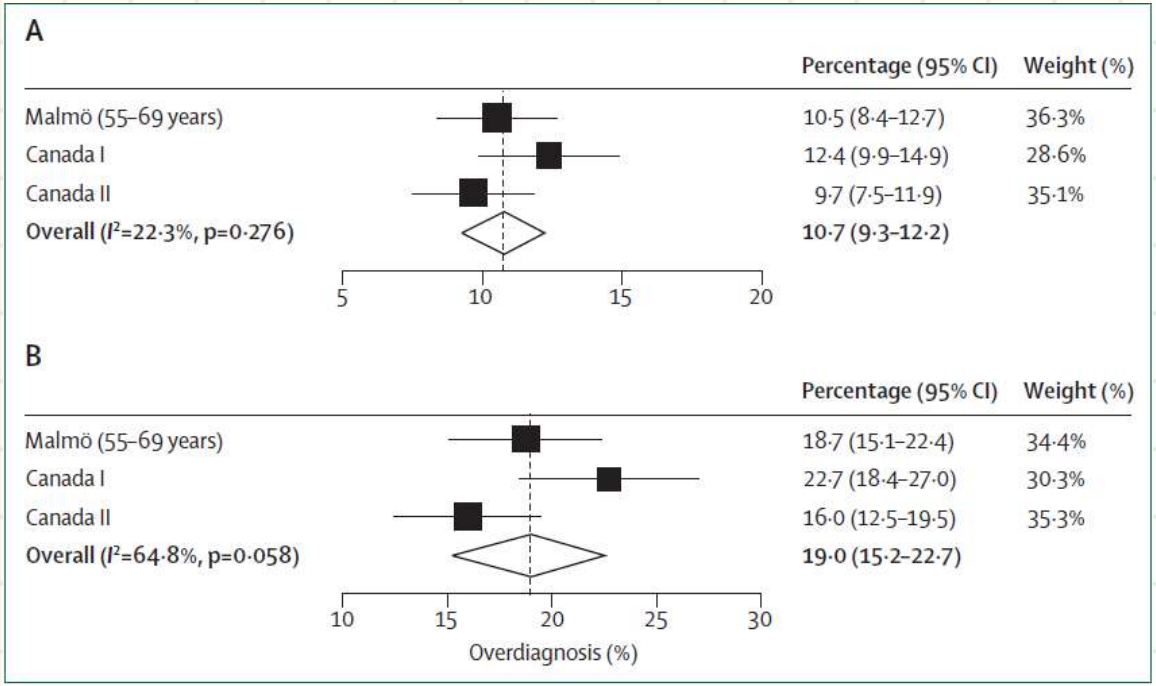
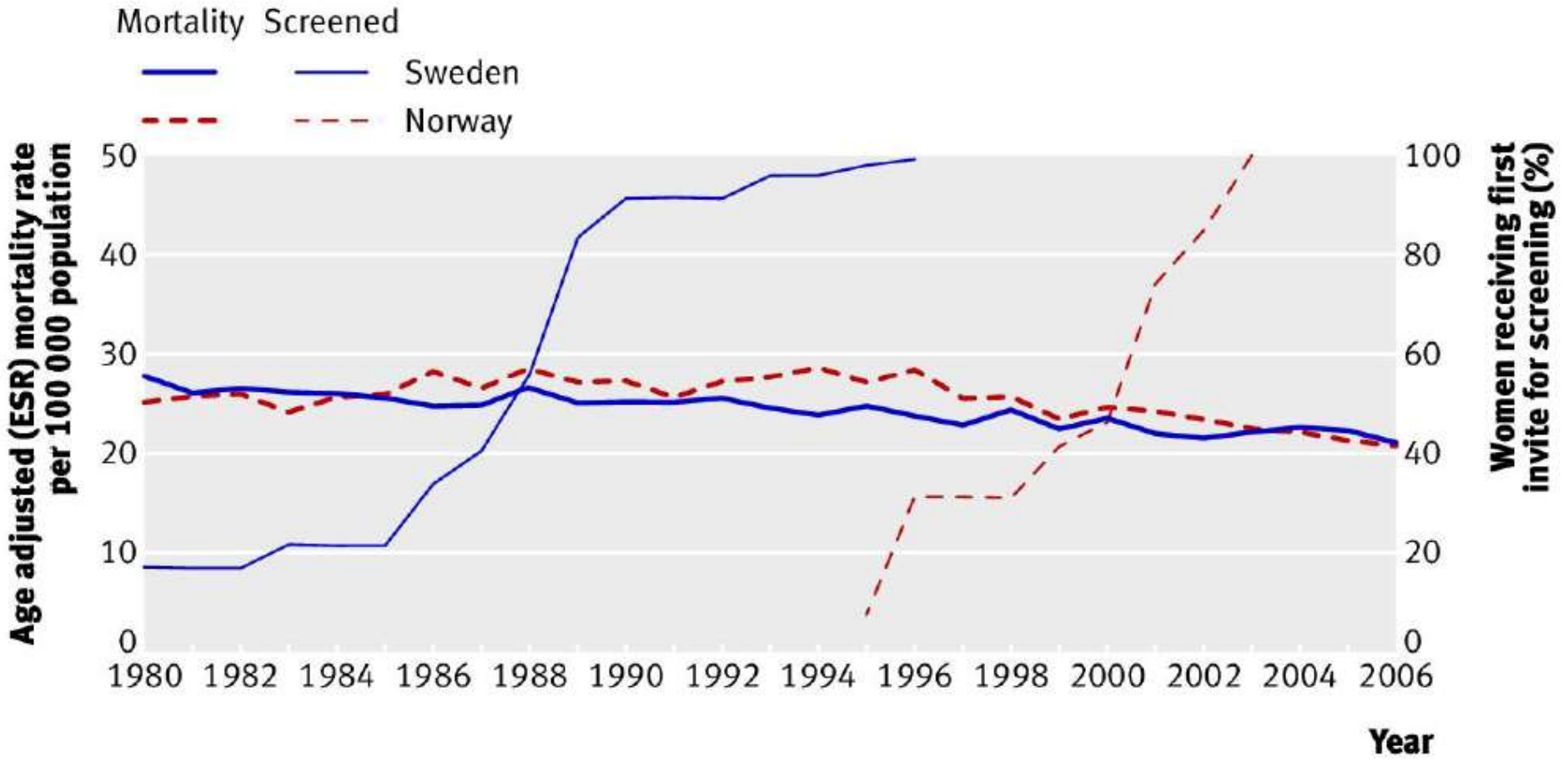


Figure 2: Meta-analysis of estimates of overdiagnosis from trials without systematic end-of-study screening of the control group

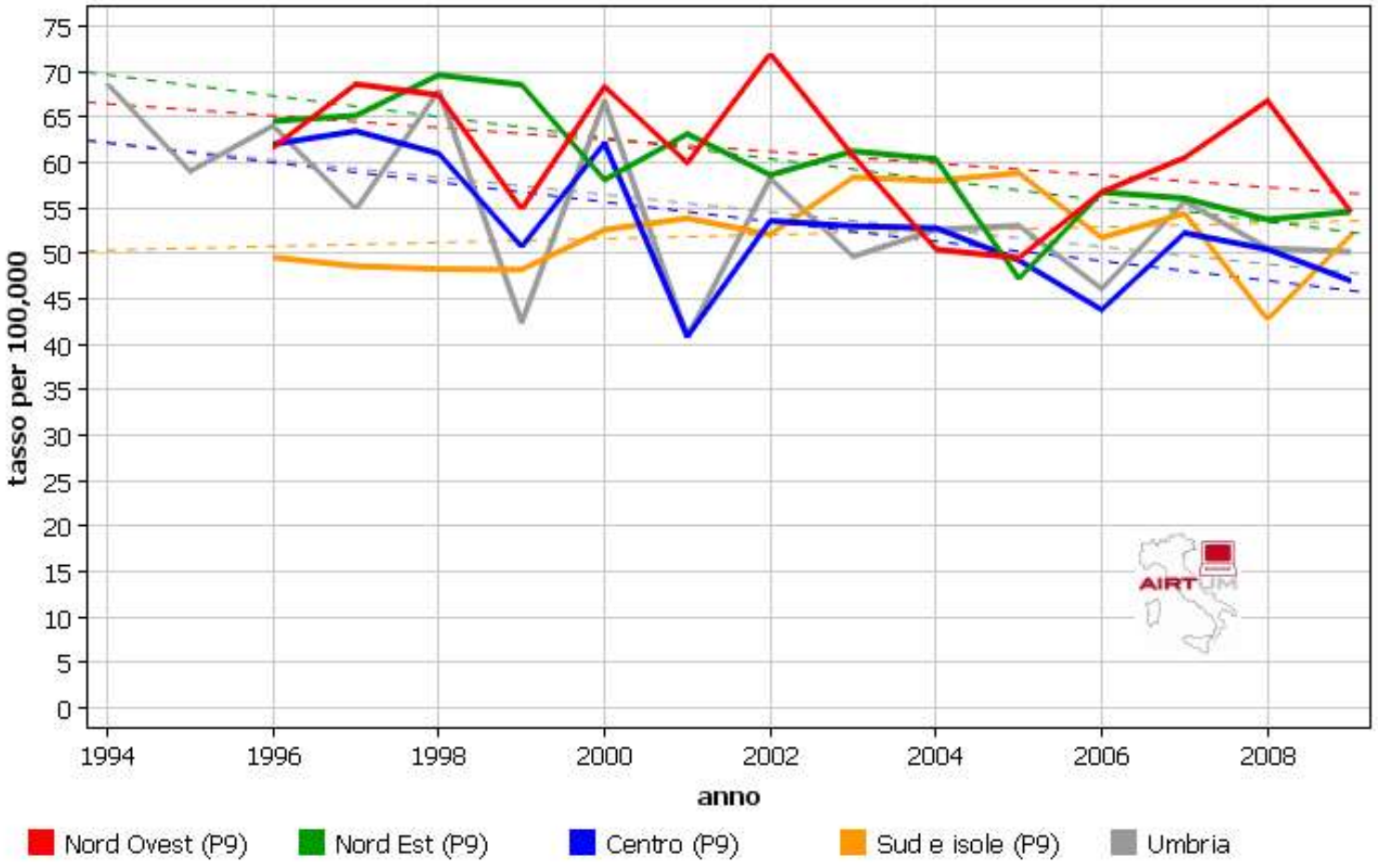
(A) Excess cancers as a proportion of cancers diagnosed over long-term follow-up in women invited for screening. (B) Excess cancers as a proportion of cancers diagnosed during the screening period in women invited for screening. Weights are from random-effects analysis.

Mortalità, incidenza, stadio e screening

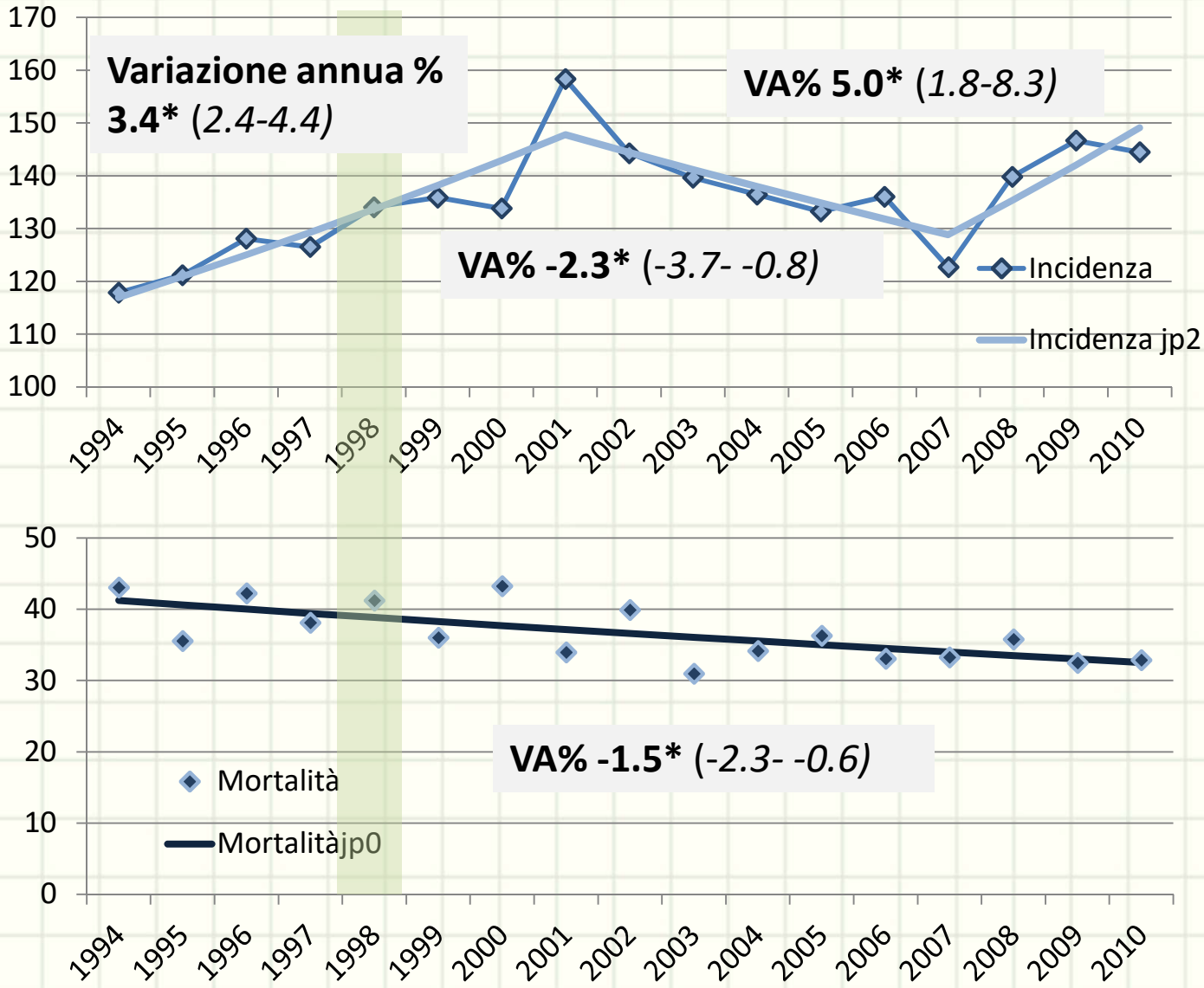


Autier P, Boniol M, Gavin A, Vatten LJ. Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. BMJ. 2011

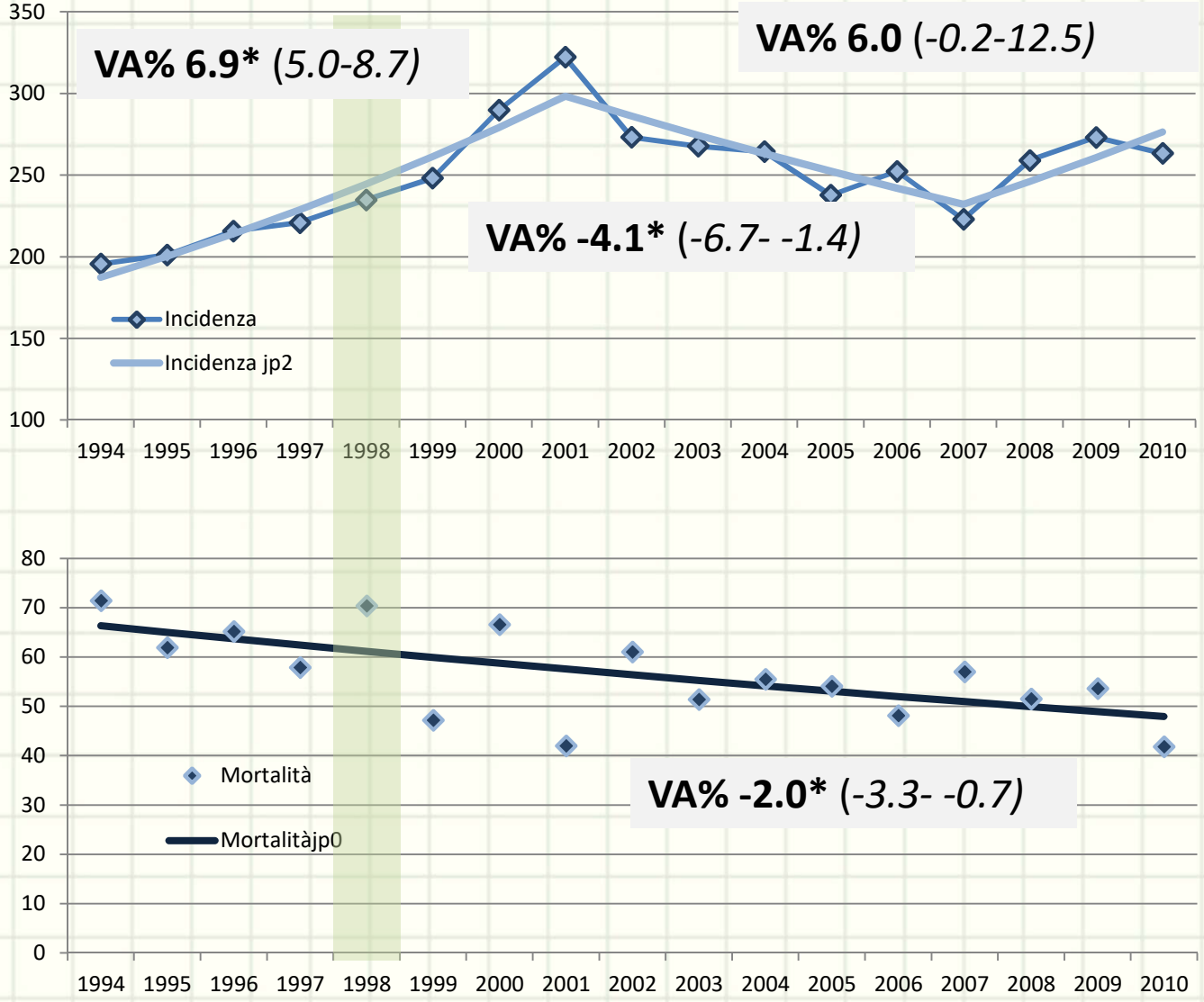
Mammella
Mortalità: TSE (Europea) età (50-69)



Contesto: Trend di incidenza e mortalità, tutte le età (tassi st. Umbria 2001)



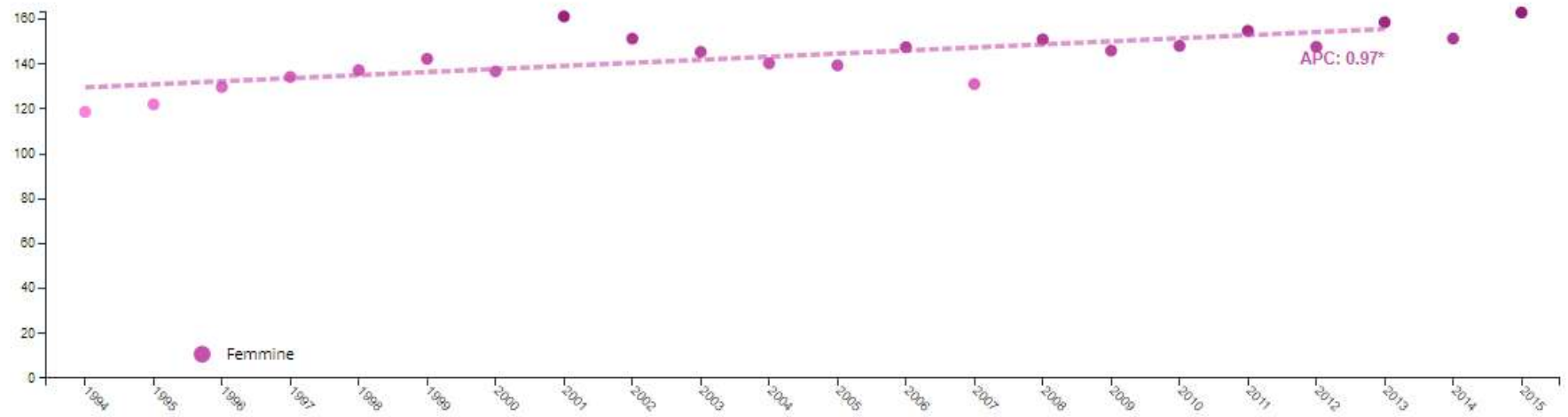
Nella classe d'età screening (50-69 anni)



Nella classe d'età 50-74 anni -2.2% *per anno (IC 95% -1.1- -3.3)

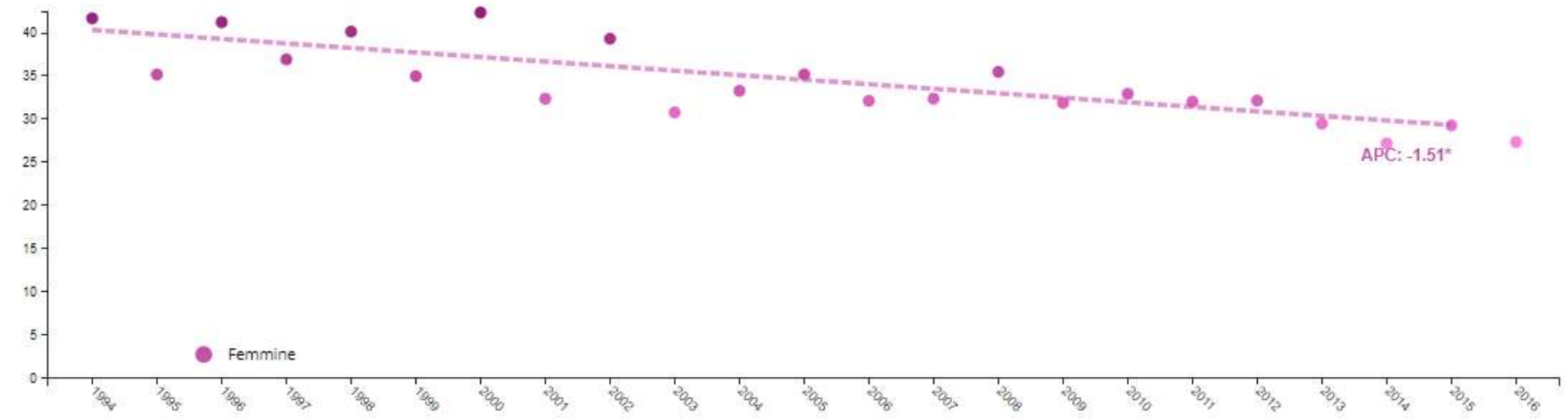
Trend temporale del tasso di incidenza dal 1994 al 2013 - mammella. 1994-2015

Tasso per 100.000 abitanti - Popolazione standard Italia 2011

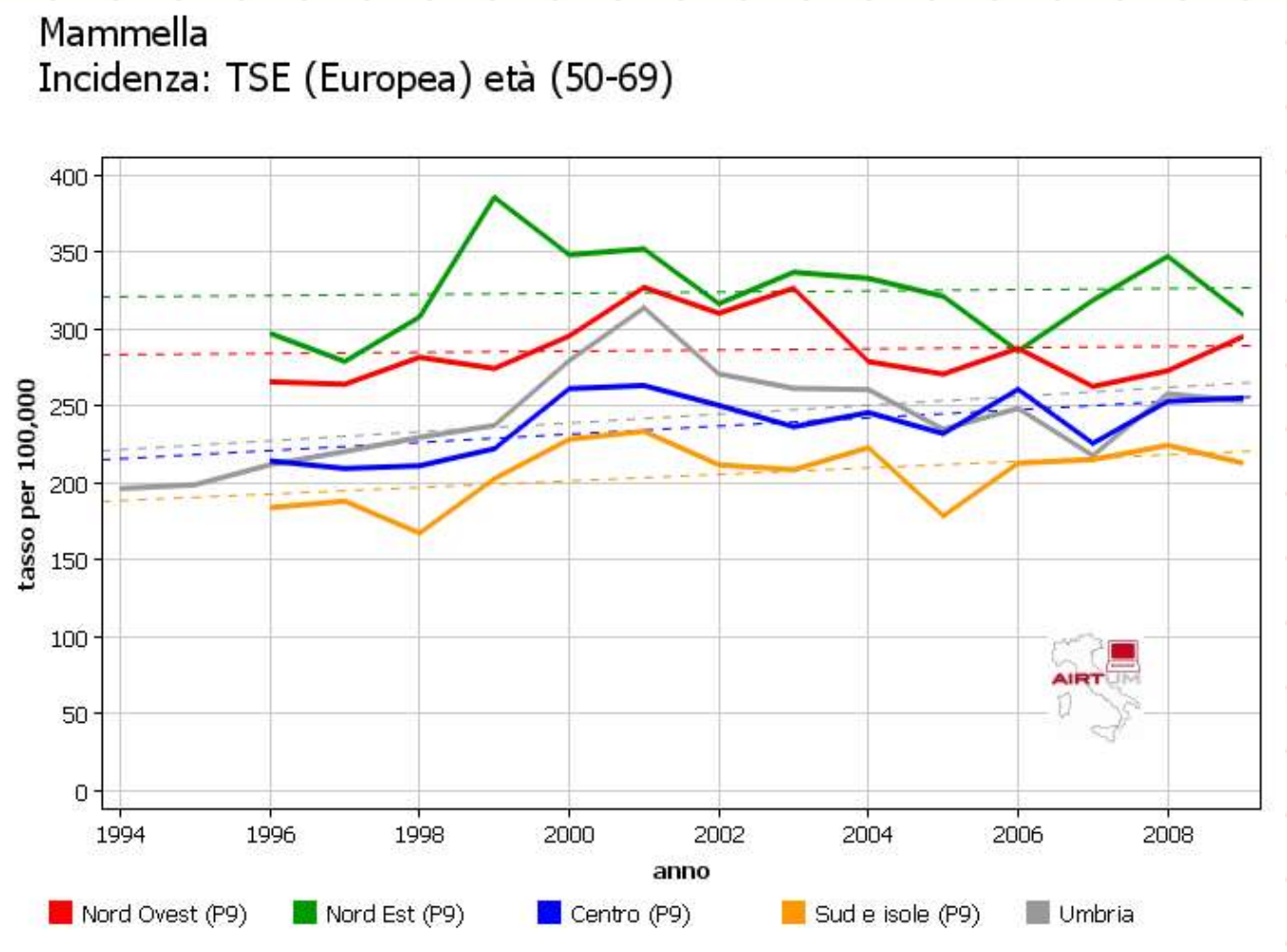


Trend temporale del tasso di mortalità dal 1994 al 2016 - mammella

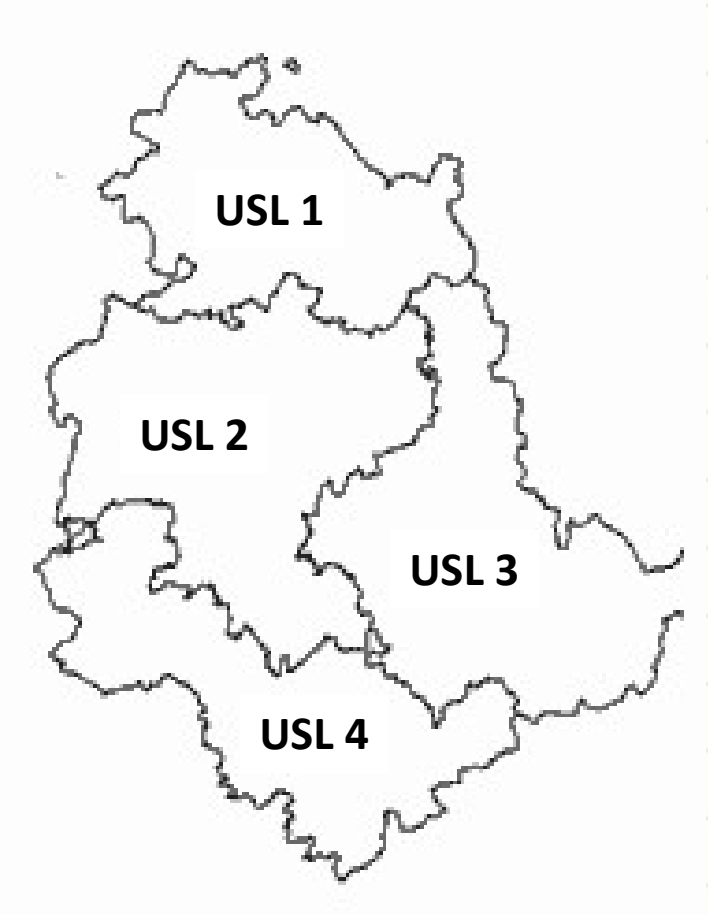
Tasso per 100.000 abitanti - Popolazione standard Italia 2011

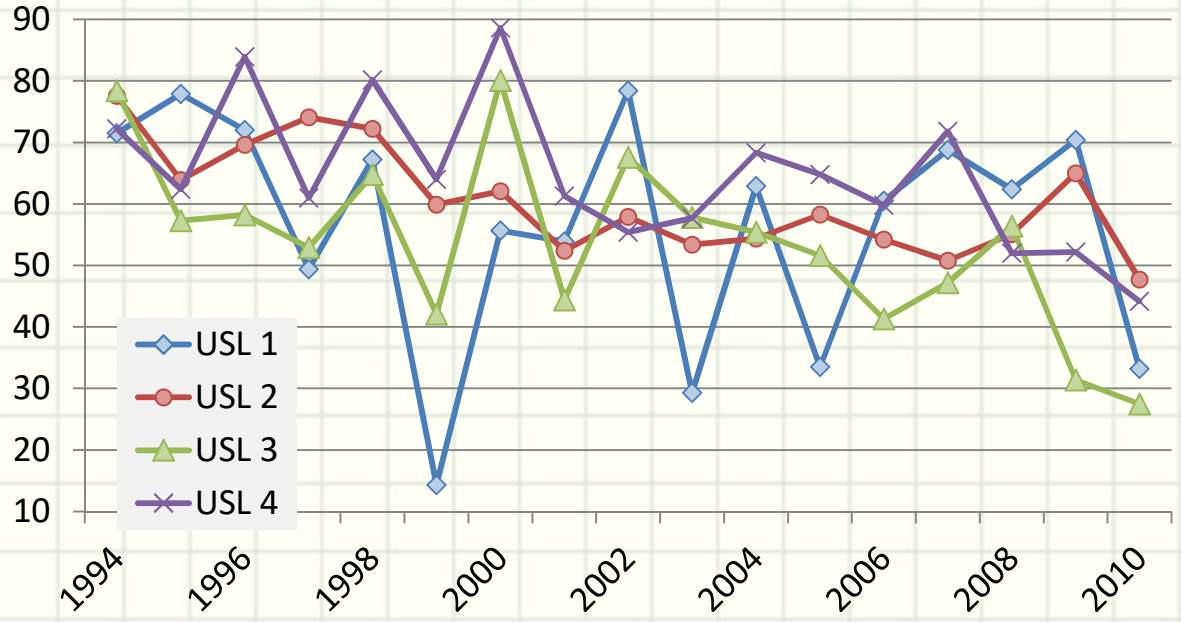


Dati AIRTum

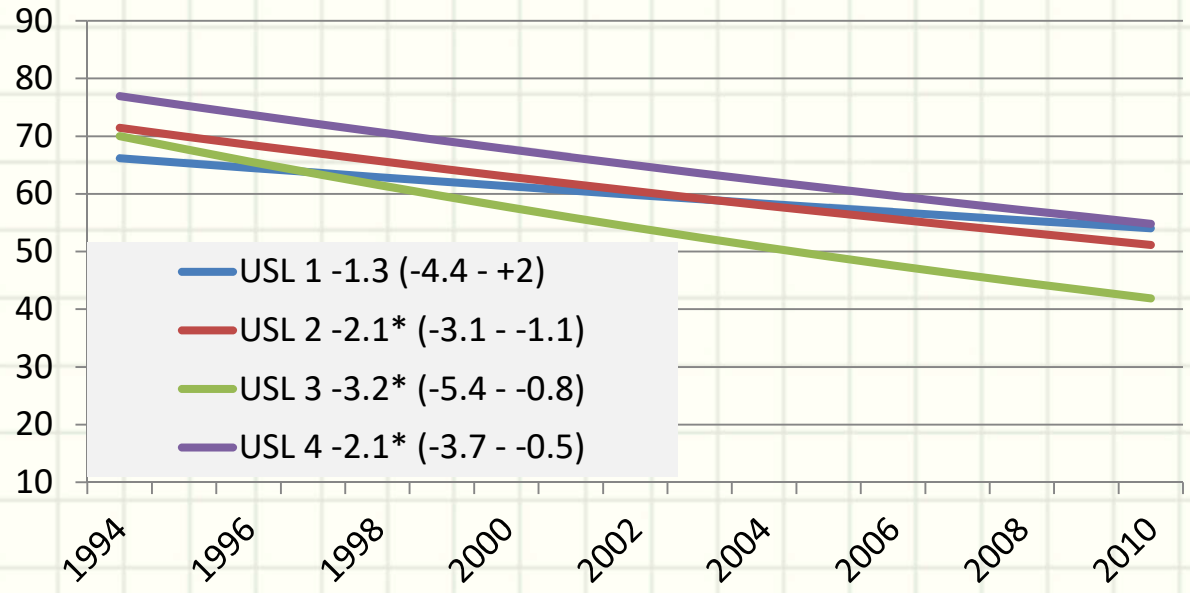

Mammella
Incidenza: TSE (Europea) età (50-69)
tasso per 100,000
400
350
300
250
200
150
100
50
0
1994
1996
1998
2000
2002
2004
2006
2008
anno
Nord Ovest (P9)
Nord Est (P9)
Centro (P9)
Sud e isole (P9)
Umbria

Vi è evidenza di un impatto diverso tra i servizi di screening delle usl?



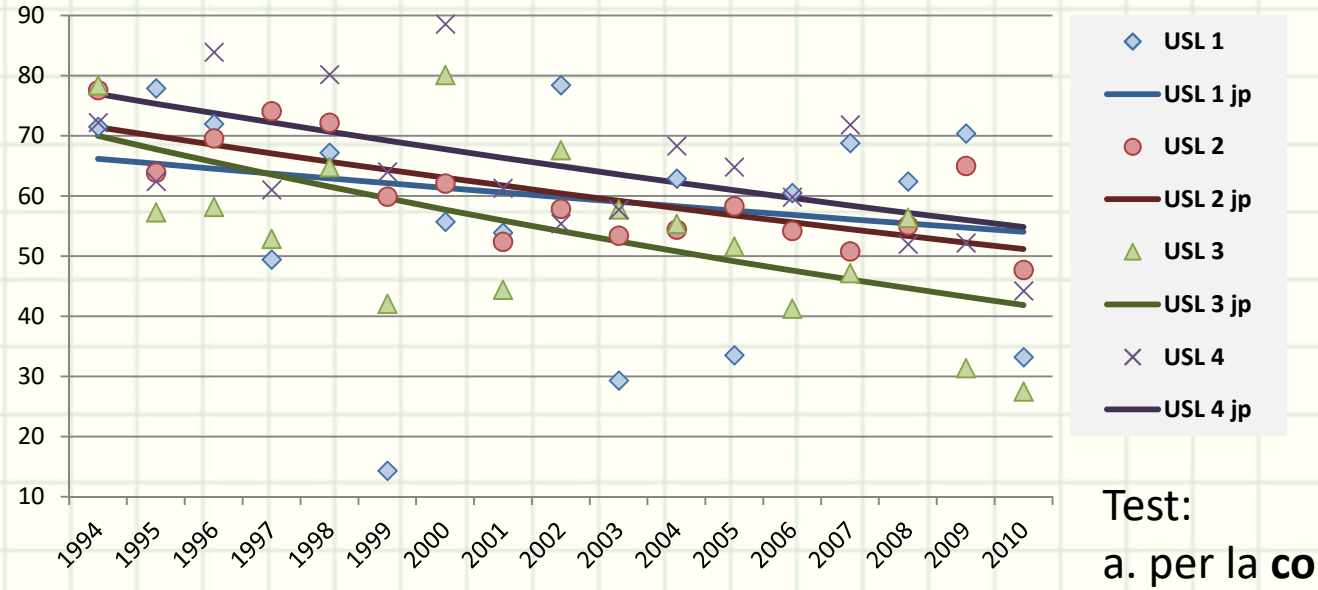


Trend di mortalità in riduzione

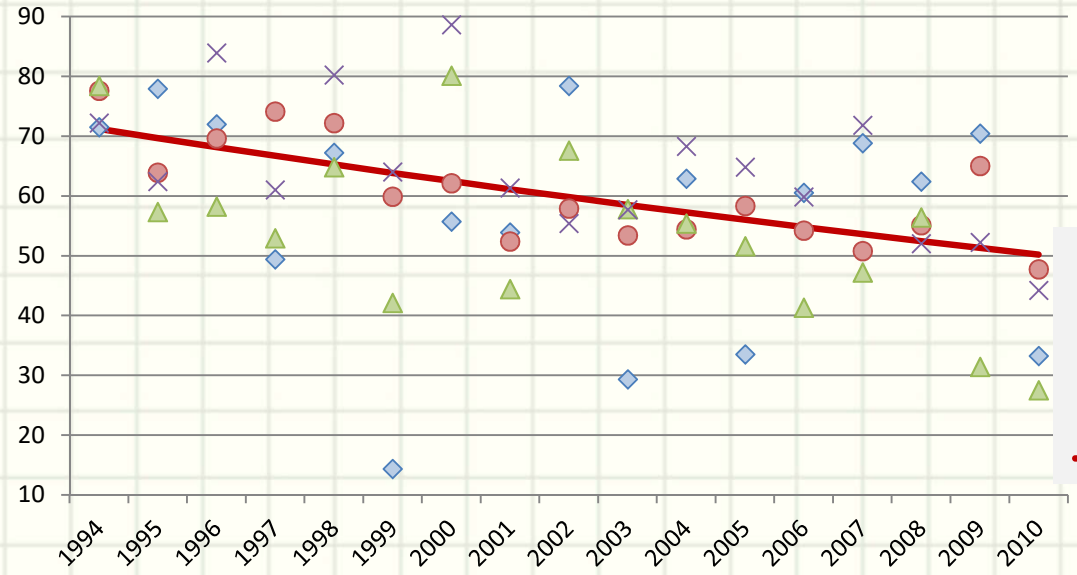


Riduzione maggiore nella USL 3 ; non significativa nella USL 1

Tassi di mortalità (st Umbria) nella classe d'età 50-74 anni per USL



Riduzione maggiore nella ex-USL 3 ; non significativa nella ex-USL 1



Test:

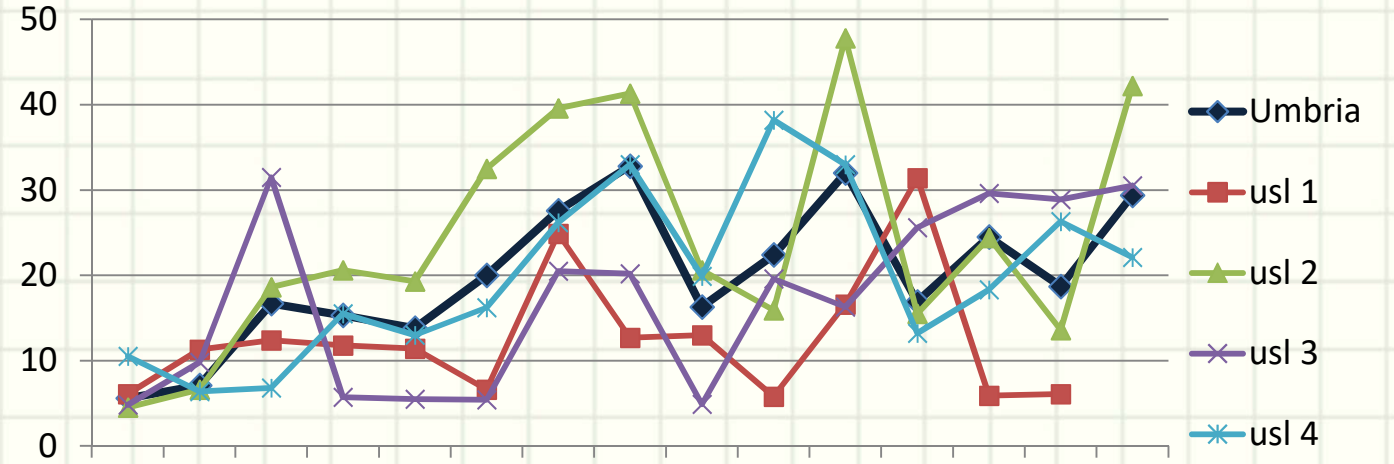
a. per la **coincidenza** dei livelli di mortalità: ns*

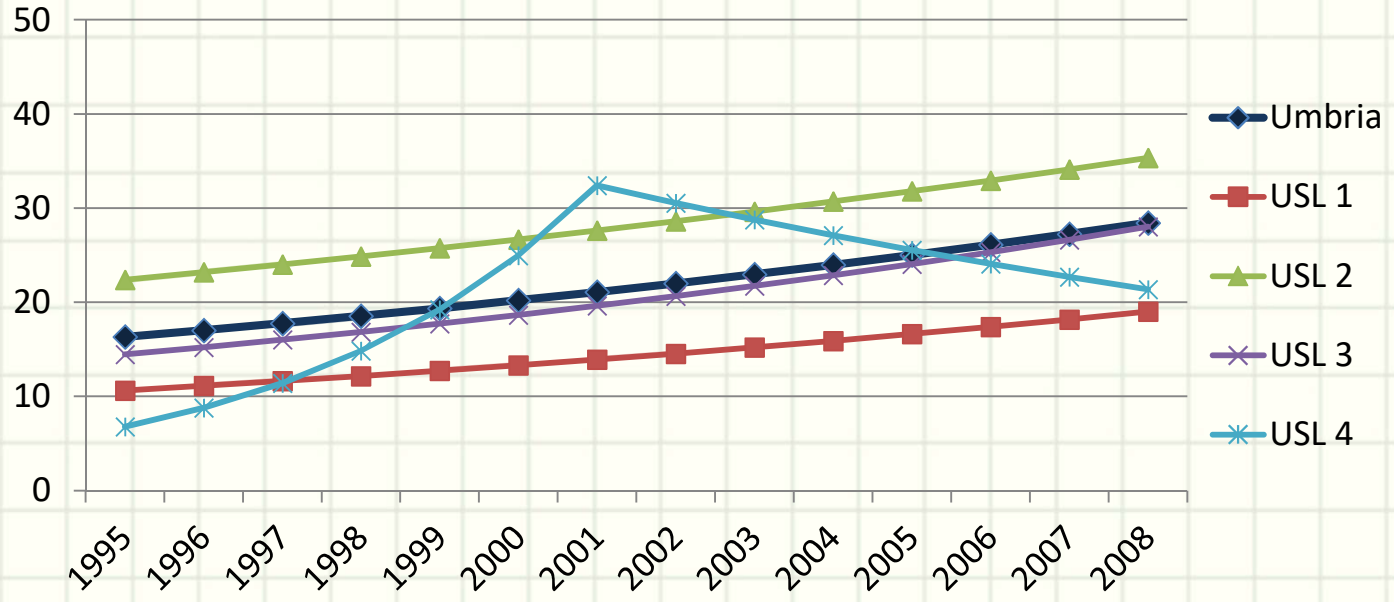
b. Per la variazione della mortalità (**parallelismo**): ns

Possiamo rappresentare il trend di mortalità con **un solo valore regionale** (VA -2.2% IC 95% -1.1- -3.3)

Altri indicatori: i carcinomi in situ

anno	% in situ
1994	*2.65*
1995	*3.43*
1996	6.95
1997	7.12
1998	5.52
1999	7.21
2000	8.59
2001	9.09
2002	5.79
2003	8.31
2004	10.42
2005	6.98
2006	9.52
2007	8.39
2008	10.29

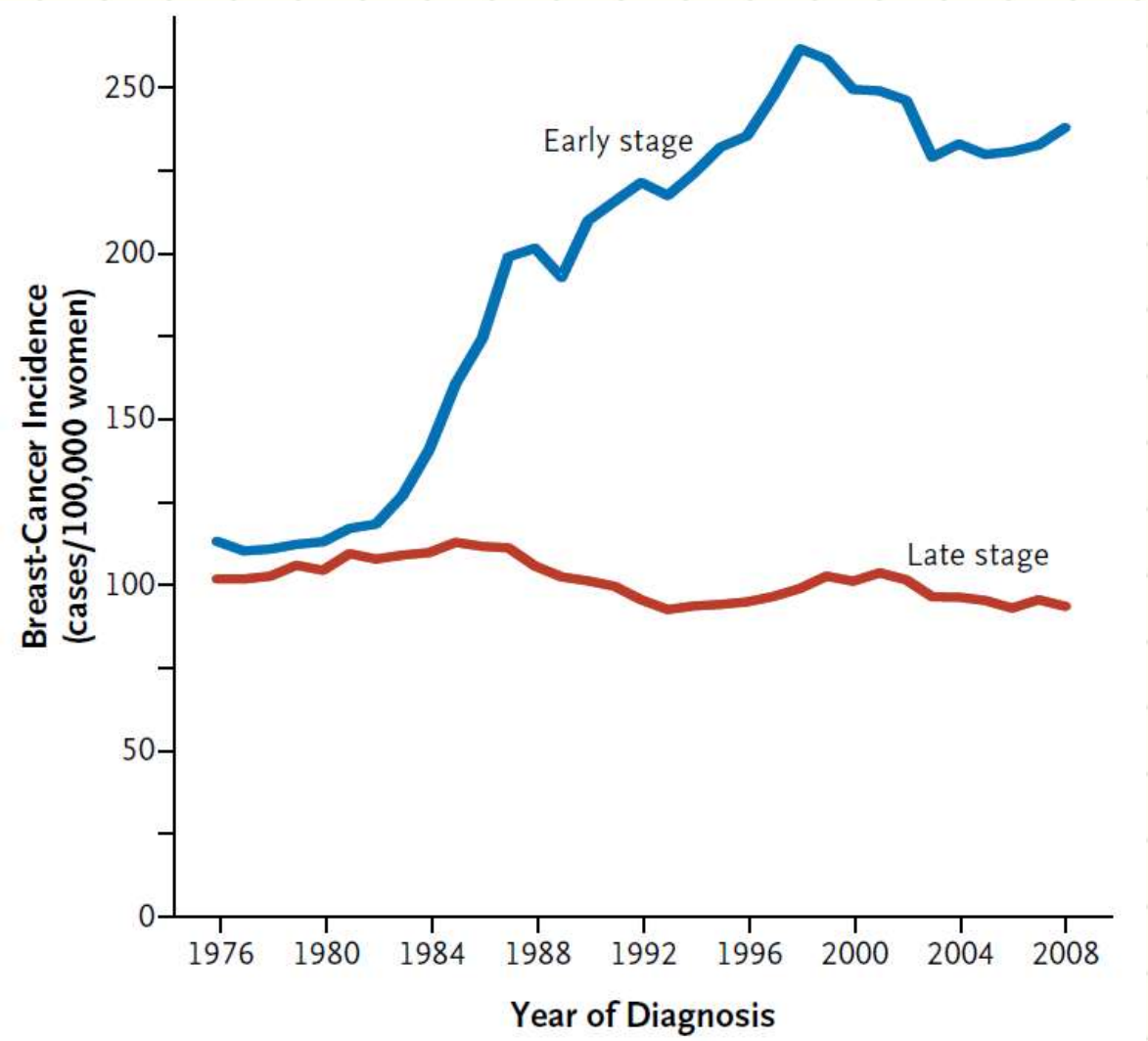




Effetti surrogati dello screening

- A decrease in the incidence of larger tumors suggests that earlier detection is occurring —
- a necessary, but not sufficient, condition for screening to result in lower mortality
- (with the second condition being that earlier treatment of these tumors must be more effective than treatment after clinical presentation).

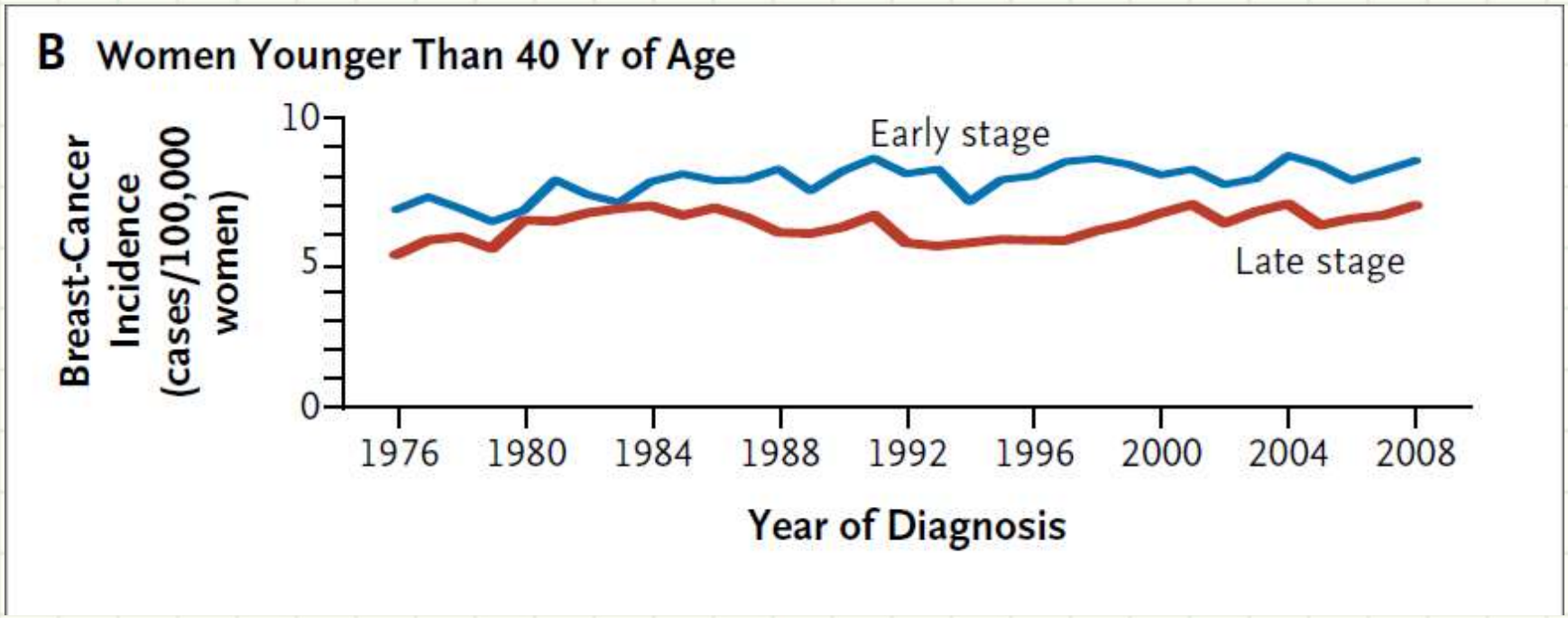
Breast-Cancer Tumor Size, Overdiagnosis, and Mammography Screening Effectiveness
H. Gilbert Welch et al. N Engl J Med 2016; 375;15



Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence.
N Engl J Med. 2012 Nov 22;367:1998-2005.

Table 1. Absolute Change in the Incidence of Stage-Specific Breast Cancer among Women 40 Years of Age or Older after the Introduction of Screening Mammography.*

Variable	Annual Breast-Cancer Incidence			Women Affected over the Three Decades†
	Before Mammography (1976–1978)	Three Decades Later (2006–2008)	Absolute Change	
	number of cases per 100,000 women			*estimated number of women*
Increase in cases of early-stage breast cancer				
DCIS	7	56	50	573,000
Localized disease	105	178	72	1,012,000
Total	112	234	122	1,585,000
Decrease in cases of late-stage breast cancer				
Regional disease	85	78	–8‡	59,000
Distant disease	17	17	0§	8,000
Total	102	94	–8	67,000



Conclusions

Despite substantial increases in the number of cases of early-stage breast cancer detected**, screening mammography has only marginally reduced the rate at which women present with advanced cancer**. Although it is not certain which women have been affected, the imbalance suggests that there is substantial **overdiagnosis, accounting for nearly a third of all** newly diagnosed breast cancers, and that **screening is having, at best, only a small effect on the rate of death from breast cancer**.

TABLE 2. Incidence[a] of Stage-Specific Breast Cancer Among Women Aged ≥40 Years, Unadjusted for Underlying Breast Cancer Temporal Trends Increase

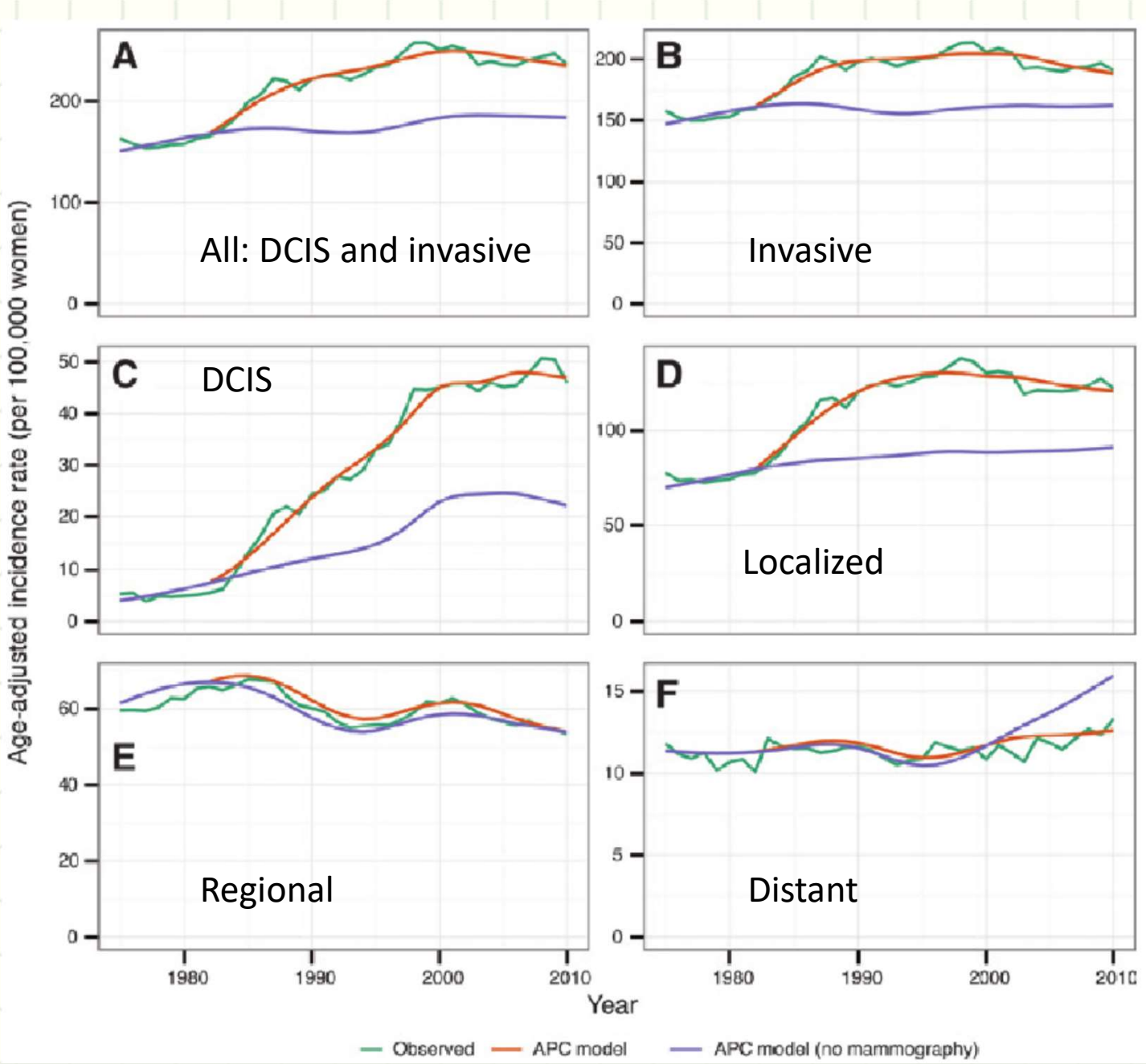
	1977 to 1979	2007 to 2009	Absolute Change	% Change
Early stage				
DCIS	6.3	58.4	52.1	827
Localized disease	106.6	181.2	74.7	70
Total	112.9	239.6	126.8	112
Late stage				
Regional	86.5	77.2	−9.3	−11
Distant	16.8	17.7	0.9	5
Total	103.3	94.9	−8.4	−8
Total invasive cancer	209.9	276.2	66.3	32
Total breast cancer	216.2	334.6	118.4	55

Tenendo conto dell'aumento di incidenza (anche di stadi avanzati) la riduzione associata alla mammografia appare rilevante

TABLE 3. Projected Incidence[a] of Stage-Specific Breast Cancer Among Women Aged ≥40 Years From 1977 Through 1979 to 2007 Through 2009, Adjusted for Underlying Temporal Trends

	1977 to 1979	Projected 2007 to 2009			
	Baseline	APC of 0.5%	APC of 1.0%	APC of 2%	APC of 1.3%
Early stage					
DCIS	6.3	7.7	8.4	11.2	9.2
Localized disease	106.6	121.3	144.0	186.4	152.6
Total	112.9	129.0	148.4	197.6	161.8
Late stage					
Regional	86.5	100.7	116.3	154.8	126.8
Distant	16.8	19.1	22.0	29.3	24.0
Total	103.3	119.8	138.4	184.1	150.8

Helvie, Mark A., et al. "Reduction in late-stage breast cancer incidence in the mammography era: Implications for overdiagnosis of invasive cancer." *Cancer* (2014).



The contribution of mammography screening to breast cancer incidence trends in the United States: an updated age-period-cohort model.

Gangnon RE et al. Cancer Epidemiol Biomarkers Prev. 2015; 24:905-12

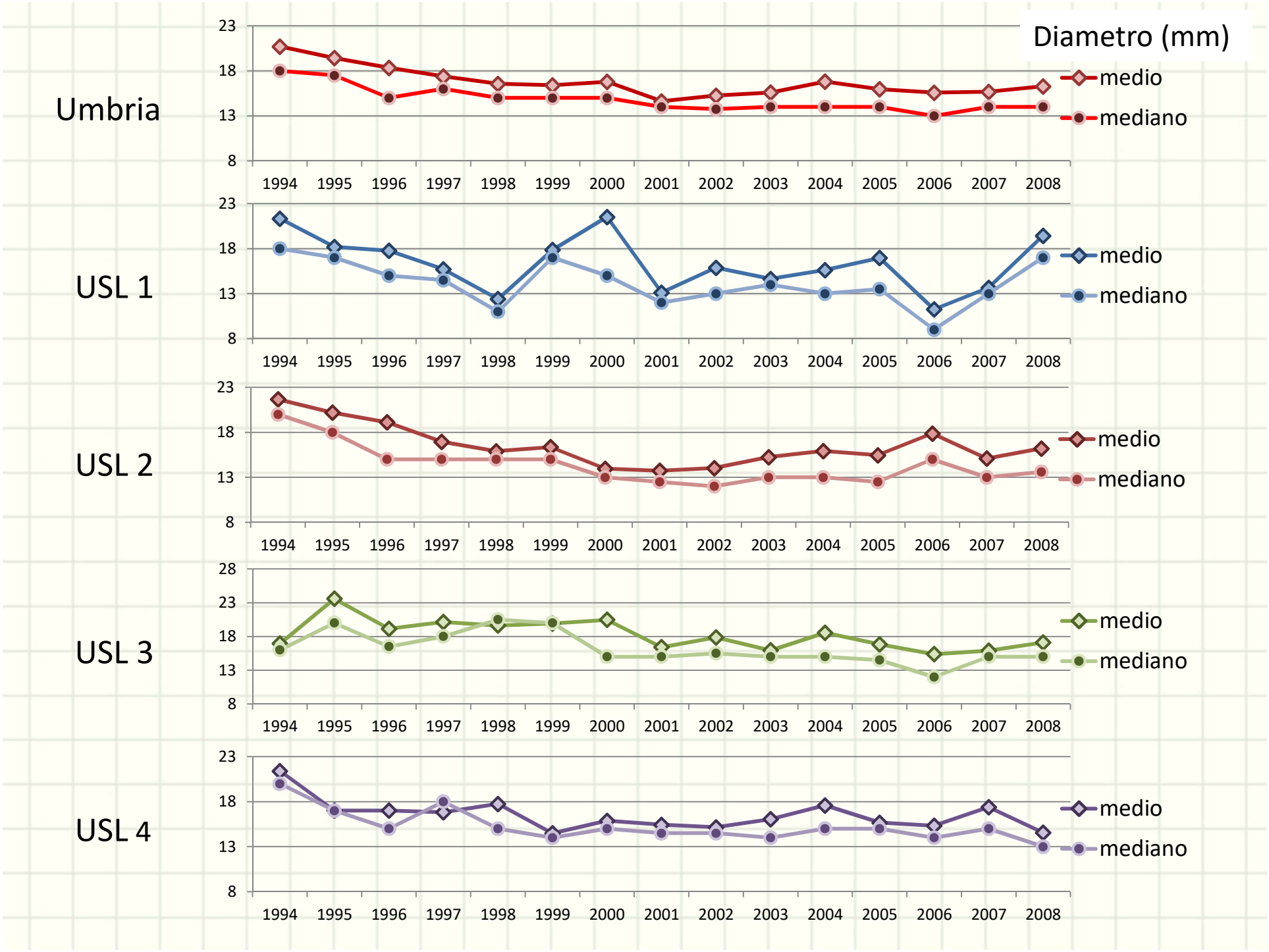
The contribution of mammography screening ...

Gangnon RE et al. Cancer Epidemiol Biomarkers Prev. 2015; 24:905-12

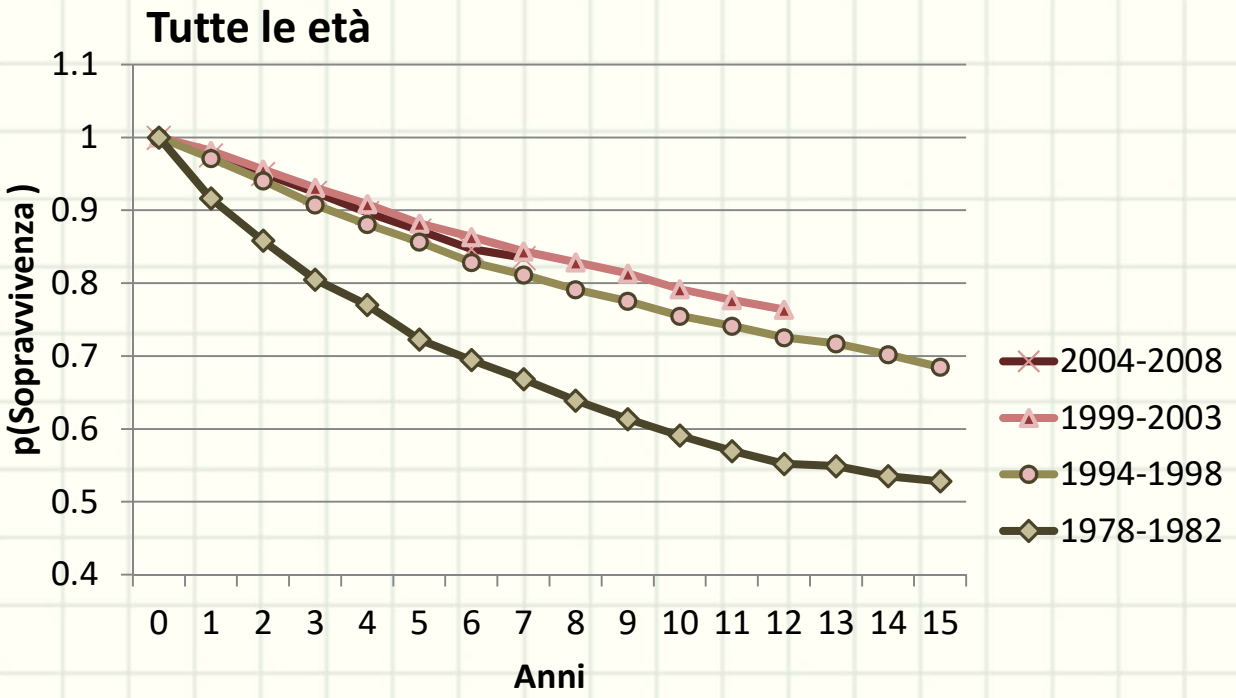
- **BACKGROUND:** The impact of screening mammography on breast cancer incidence is difficult to disentangle from cohort- and age-related effects on incidence.
- **METHODS:** We developed an age-period-cohort model of ductal carcinoma in situ (DCIS) and invasive breast cancer incidence in U.S. females using cancer registry data. Five functions were included in the model to estimate stage-specific effects for age, premenopausal birth cohorts, postmenopausal birth cohorts, period (for all years of diagnosis), and a mammography period effect limited to women ages ≥ 40 years after 1982. Incidence with and without the mammography period effect was calculated.
- **RESULTS: More recent birth cohorts have elevated underlying risk compared with earlier cohorts** for both pre- and postmenopausal women. Comparing models with and without the mammography period effect showed that overall **breast cancer incidence would have been 23.1% lower in the absence of mammography in 2010** (95% confidence intervals, 18.8-27.4), including 14.7% (9.5-19.3) lower for invasive breast cancer and 54.5% (47.4-59.6) lower for DCIS. **Incidence of distant-staged breast cancer in 2010 would have been 29.0% (13.1-48.1) greater in the absence of mammography screening**.
- **CONCLUSIONS:** Mammography contributes to markedly elevated rates of DCIS and early-stage invasive cancers, but also contributes to substantial reductions in the incidence of metastatic breast cancer.
- **IMPACT:** Mammography is an important tool for reducing the burden of breast cancer, but future work is needed to identify risk factors accounting for increasing underlying incidence and to distinguish between indolent and potentially lethal early-stage breast cancers that are detected via mammography.

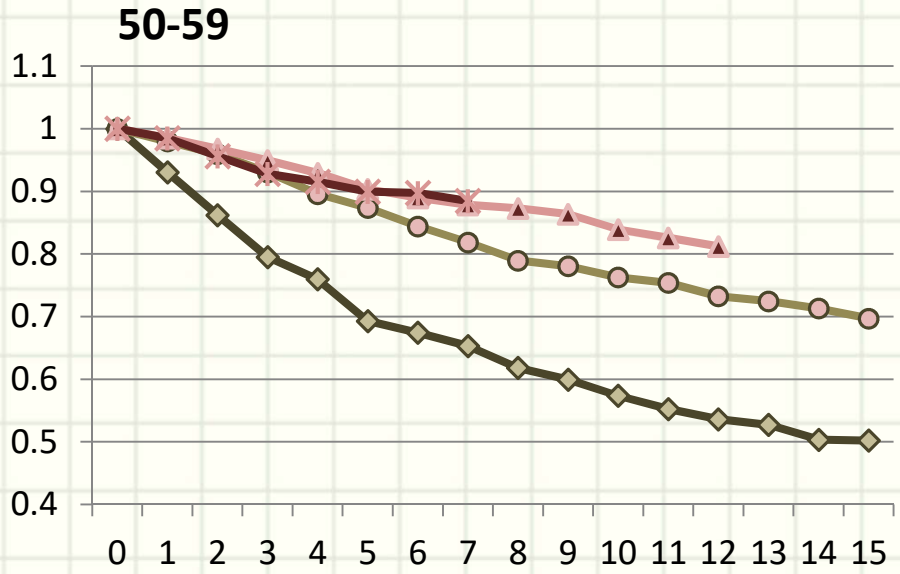
Tasso di incidenza di carcinomi M+ in Umbria per classe d'età (periodo 1994-2009)

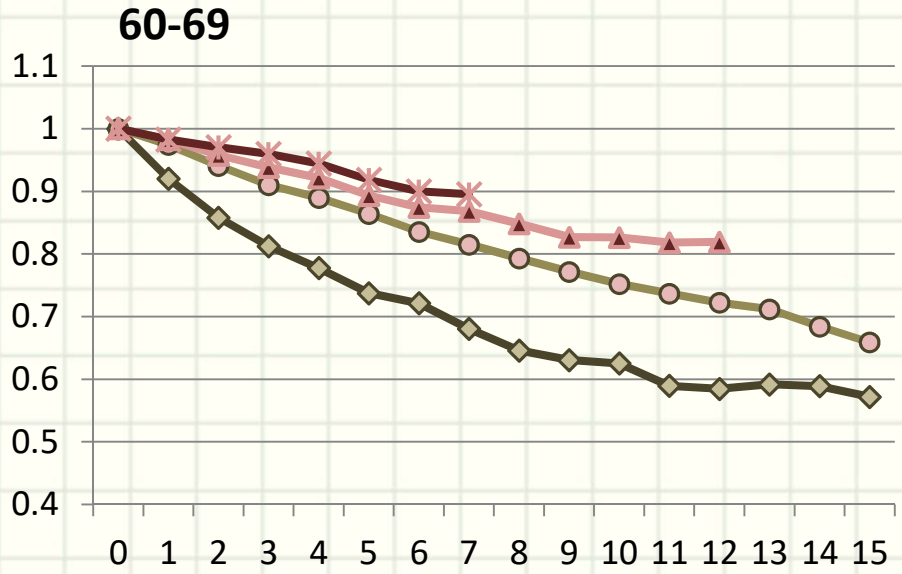
Screening	**Età**	**APC**	**IC 95%**	
No(?)	<40	***+6.2***	-8.2	+22.7
$S_{opportunistico}$	40-49	***+1.0***	-3.9	+6.2
S_{misto}	**50-59**	***-3.7***	-8.5	+1.5
S_{misto}	**60-69**	***-3.0***	-6.5	+0.6
$S_{opportunistico*}$	70-79	***-3.3***	-7.2	+0.7
No(?)	80+	***+4.9***	-8.9	+20.9
	Tutte le età	***-2.2***	-5.3	+1.1


Diametro (mm)
Umbria
USL 1
USL 2
USL 3
USL 4
medio
mediano
1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008
8 13 18 23 28

Sopravvivenza relativa







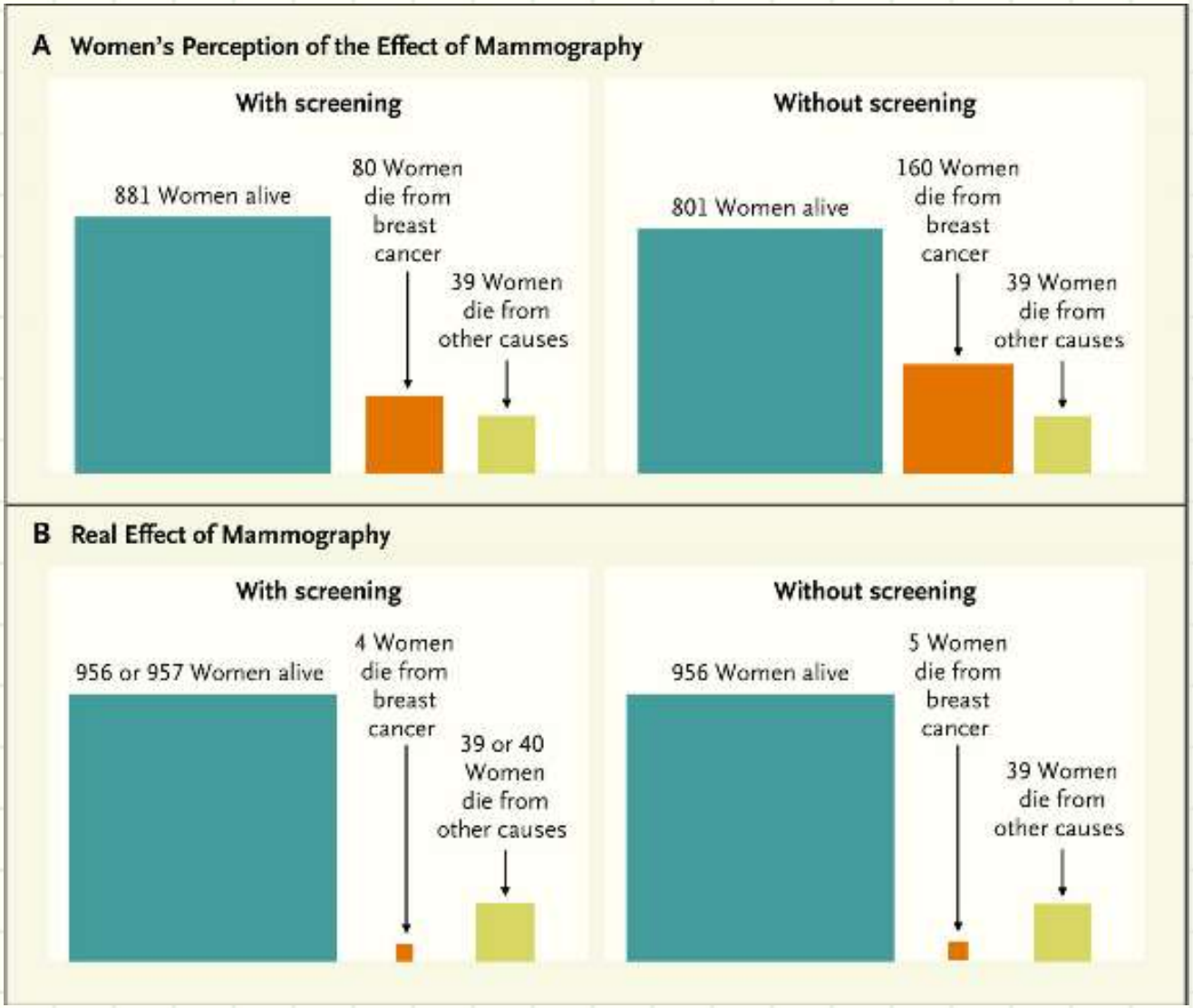
Attualità della discussione

- I trial analizzati sono ormai datati
- Il trattamento del cancro della mammella si è modificato
- L'anticipazione diagnostica ottenuta mediante lo screening è ancora determinante per la guarigione?
- Lo screening ha perso in parte o del tutto l'efficacia dimostrata nei trial ?
- Rimane un ragionamento plausibile con qualche supporto dagli studi ecologici

The impact of advances in treatment on the efficacy of mammography screening. Jatoi I. Prev Med. 2011 Jun 23.

The author argues that, for screening to be beneficial:

- the **treatment of screen-detected cancers must be more effective than that of clinically-detected** cancers.
- …as **breast cancer treatments improve over time, both the absolute and relative benefits of screening will diminish**.
- This is evident in the overview of the nine successive mammography screening trials, …
- Additionally, population-based studies seem to suggest that the benefit of mammography screening is diminishing as treatments continue to improve



U.S. Women's Perceptions of the Effects of Mammography Screening on Breast-Cancer Mortality as Compared with the Actual Effects

Clinical decisions. Mammography Screening for Breast Cancer

Smith RA, Kerlikowske K, Miglioretti DL, Kalager M.N Engl J Med. 2012 Nov 22;367

- Option 1. Recommend Screening Mammography Starting at the Age of 40
- Option 2. Recommend Screening Mammography Starting at the Age of 50
- Option 3. Do Not Recommend Screening Mammography

- Estimates of overdiagnosis have ranged from 0 to more than 50%, but the rates are small (<10%) in studies that properly adjust for lead time and trends in incidence.
- We should also consider the harms associated with electing not to be screened before the age of 50.

A recent case series showed that women whose breast cancer was not diagnosed by mammography

- were more likely to be diagnosed with a **stage II or higher** tumor than were women in whom breast cancer was diagnosed by mammography (66% vs. 27%) and
- were more likely to have a **mastectomy** (47% vs. 25%);
- undergo surgery, **radiation therapy, and chemotherapy** (59% vs. 31%); and
- have poorer 5-year survival rates

Option 2

Another school of thought discourages initiation of screening until the age of 50, emphasizing that

- the 10-year risk of breast cancer is lower when a woman is in her 40s than when she is in her 50s
- that mammography reduces the risk of death from breast cancer by only 15%,
- that **1904 women 40 to 49 years of age need to be invited to be screened over a period of 11 to 20 years to save one life**, and
- that the harms, principally false positive findings, are considerable

- One school of thought asserts that progress in therapy has eclipsed the benefit of early detection and that harms associated with screening are excessive and outweigh the benefits

Conclusioni

- Lo screening mammografico contribuisce alla riduzione della mortalità
- Tuttavia il contributo al controllo della malattia è moderato /modesto
- Il miglioramento del trattamento fornisce il maggiore contributo al trend di mortalità
- Elementi di flessibilità potrebbero migliorare l'efficacia dello screening organizzato (mammella densa)
- Lo screening al di fuori della classe d'età 50-69 presenta elementi di dubbio più marcati
- Lo screening è associato a sovra-diagnosi e sovra-trattamento e quindi determina beneficio e danno
- Sostituire lo screening organizzato con l'opportunistico comporta un elevato rischio di maggiore inappropriatezza e disequità
- La rivalutazione del beneficio in relazione ai progressi terapeutici è importante ma richiederà anni

Aggregazione di test

Addizione

- Mammografia + ecografia
- Mammografia + risonanza magnetica

Selezione

- Mammografia
- Ecografia in caso di mammella densa

Preferenza/offerta

- FIT
- Sigmoidoscopia
- Colonscopia
- Esame virtuale

Garcia EM, Storm ES, Atkinson L, Kenny E, Mitchell LS. Current breast imaging modalities, advances, and impact on breast care. Obstet Gynecol Clin North Am. 2013 Sep;40(3):429-57.

- Ultrasound and magnetic resonance imaging (MRI) are widely available adjunctive studies for women with suspicious mammographic or clinical findings, and MRI is a screening tool for women with specific increased risks for breast cancer.

.

Mahoney MC, Newell MS. Screening MR imaging versus screening ultrasound: pros and cons. Magn Reson Imaging Clin N Am. 2013 Aug;21:495-508.

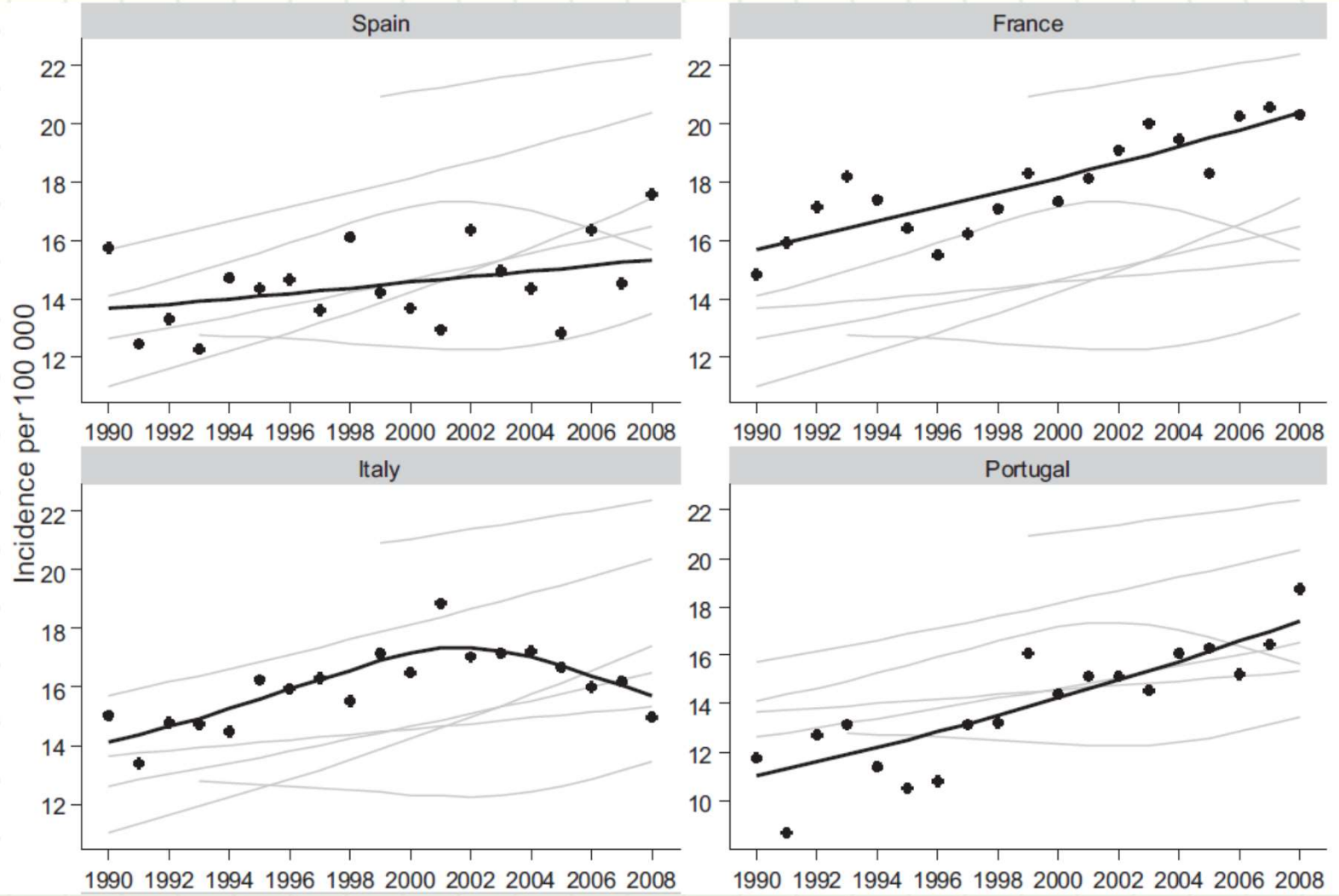
- Data support greater sensitivity of MR imaging compared with mammography and ultrasound in high-risk populations, in particular BRCA 1 and BRCA 2 carriers.
- Screening ultrasound improves cancer yield versus mammography alone in high-risk patients and in patients with dense breasts and is less expensive.
- Drawbacks include low positive predictive value, operator dependence, and significant physician time expenditure

Donne in età <50 anni

- Breast density increases breast cancer incidence significantly [19,20].
- At the same time, high mammographic density impairs the sensitivity of mammography [19-22], but far less the sensitivity of MRI [23]….
- Breast density is high or very-high in about 50-74% of women between 40 to 49 years of age, whereas only 20-44% of women in their 60s have dense or extremely dense breast tissue

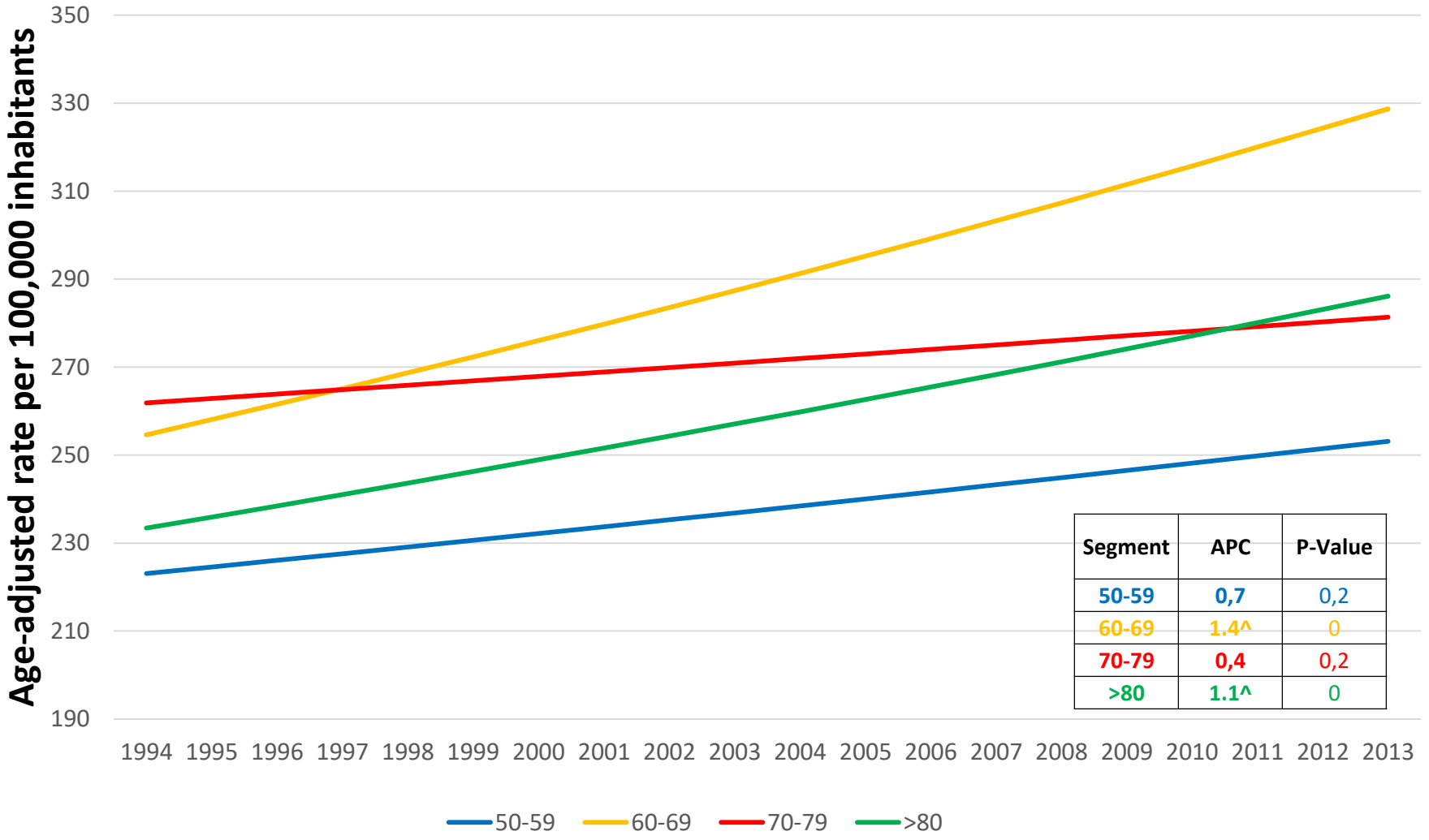
Trends in incidence of breast cancer among women under 40 in seven European countries: A GRELL cooperative study.

Leclerc B et al 2013 Cancer epidemiology 2013



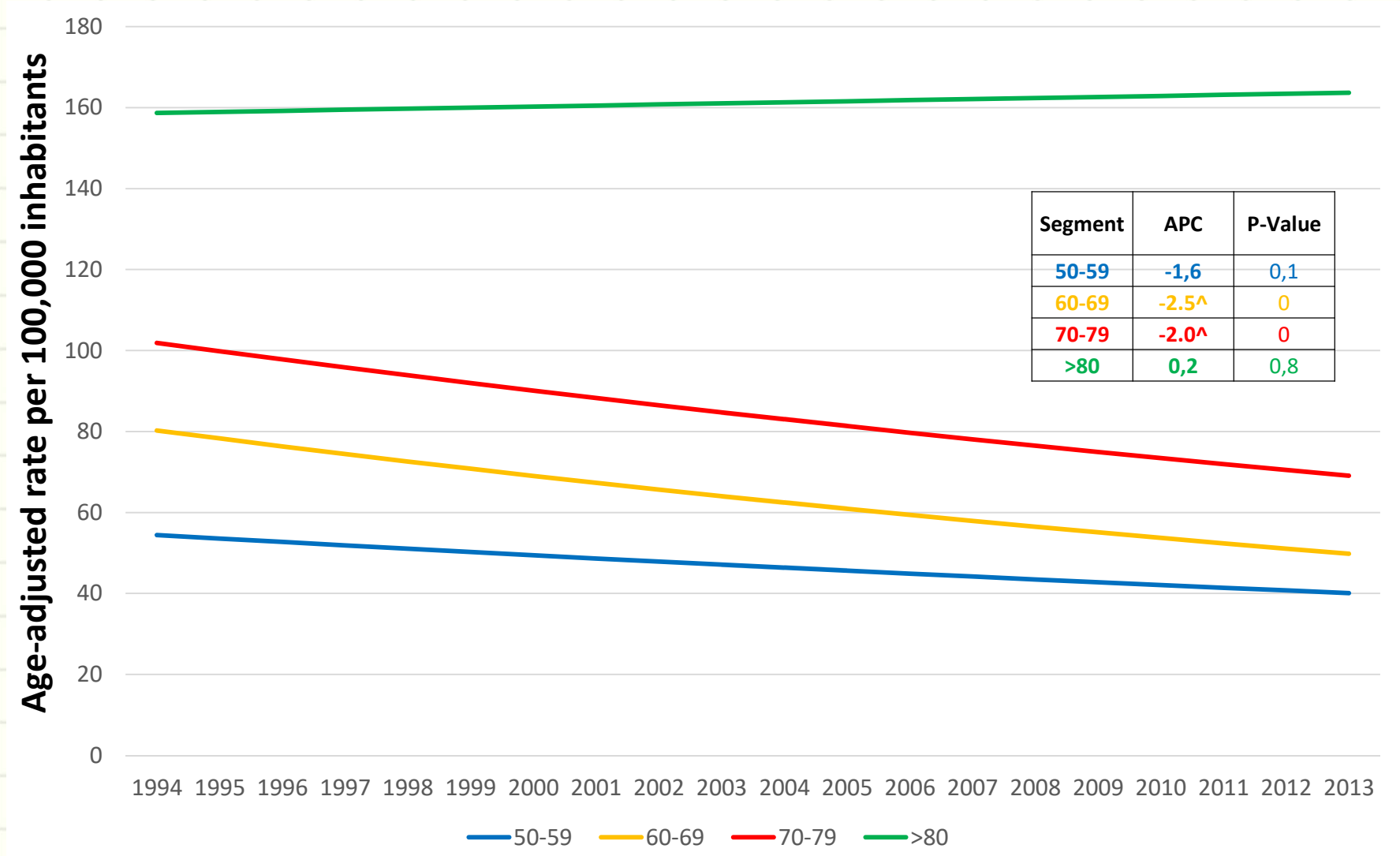
LA MALATTIA NELL'ANZIANA

Trend di **Incidenza** in Umbria per classi d'età



Segment	APC	P-Value
50-59	0,7	0,2
60-69	1.4^	0
70-79	0,4	0,2
>80	1.1^	0

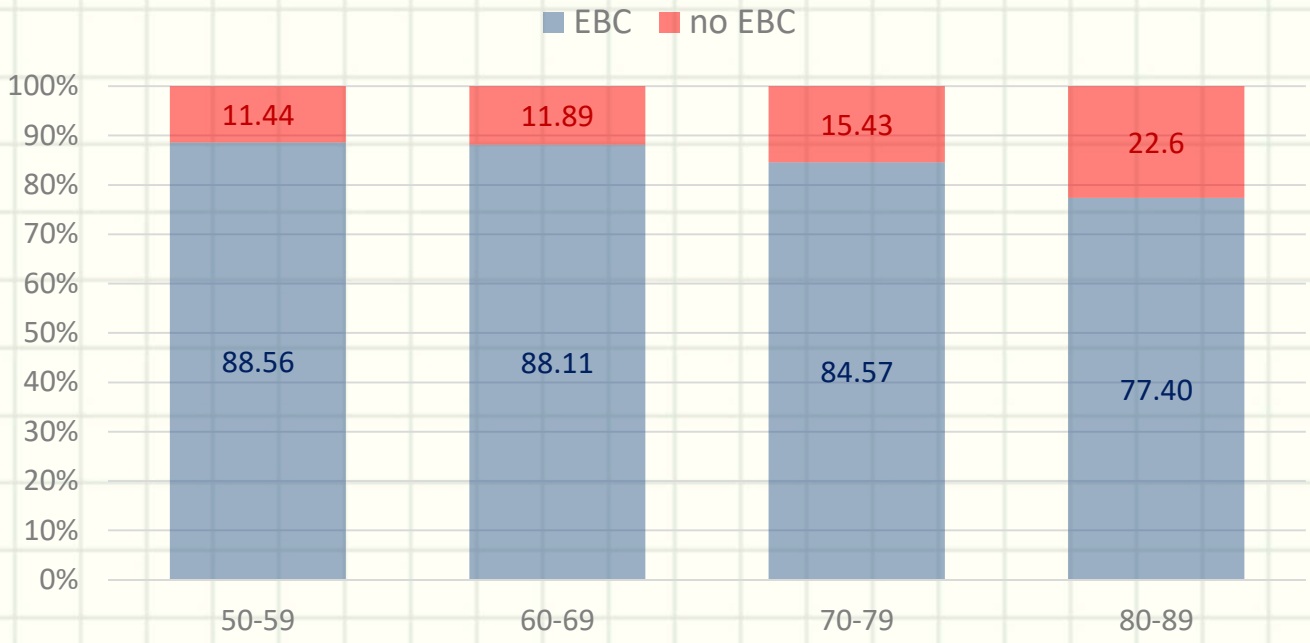
Trend di **Mortalità** in Umbria per classi d'età



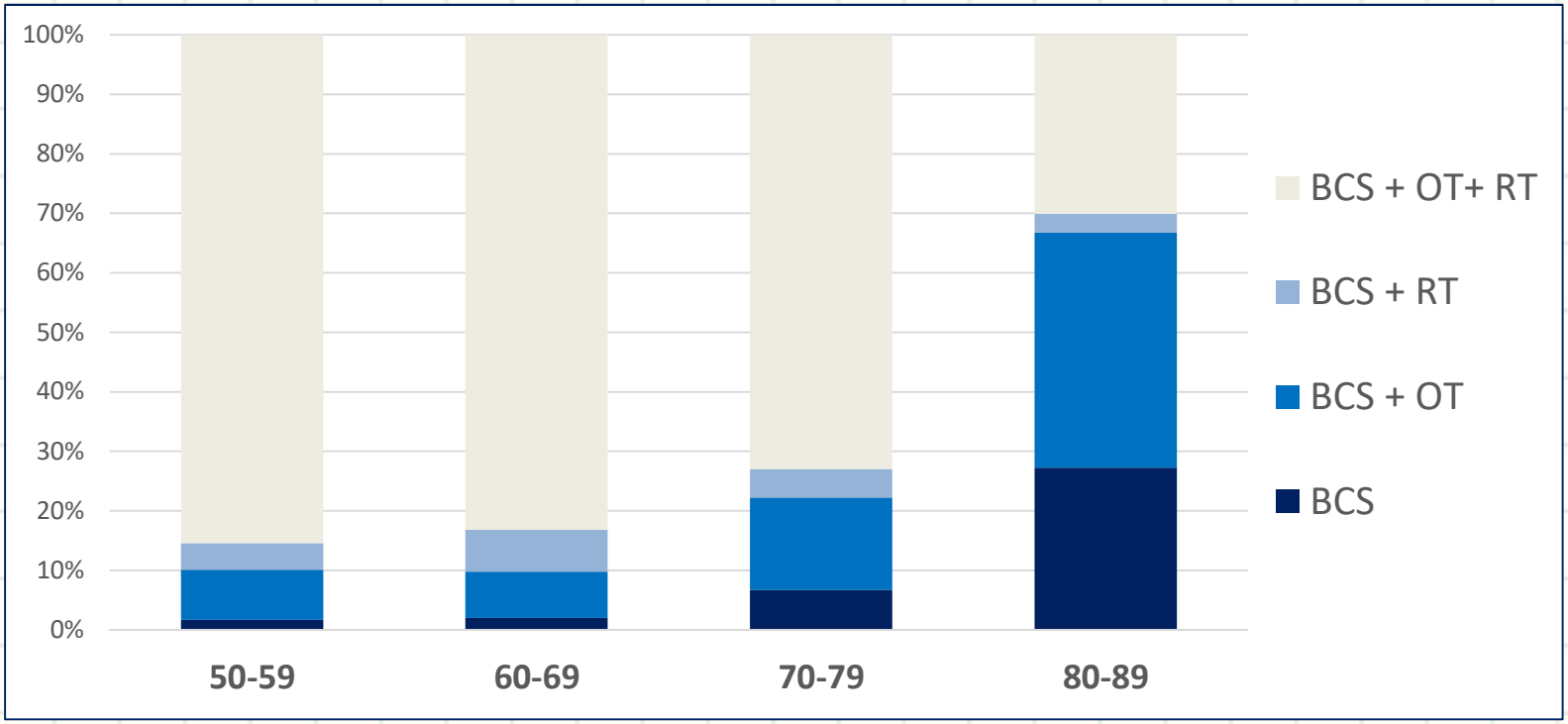
Segment	APC	P-Value
50-59	-1,6	0,1
60-69	-2.5^	0
70-79	-2.0^	0
>80	0,2	0,8

Early Breast Cancer (T1-2 e N0-1)

EBC	50-59		60-69		70-79		80-89		totale	
	n	%	n	%	n	%	n	%	n	%
si	1084	88,56	1267	88,11	932	84,57	322	77,40	**3605**	79,95
no	140	11,44	171	11,89	170	15,43	94	22,60	**575**	20,05

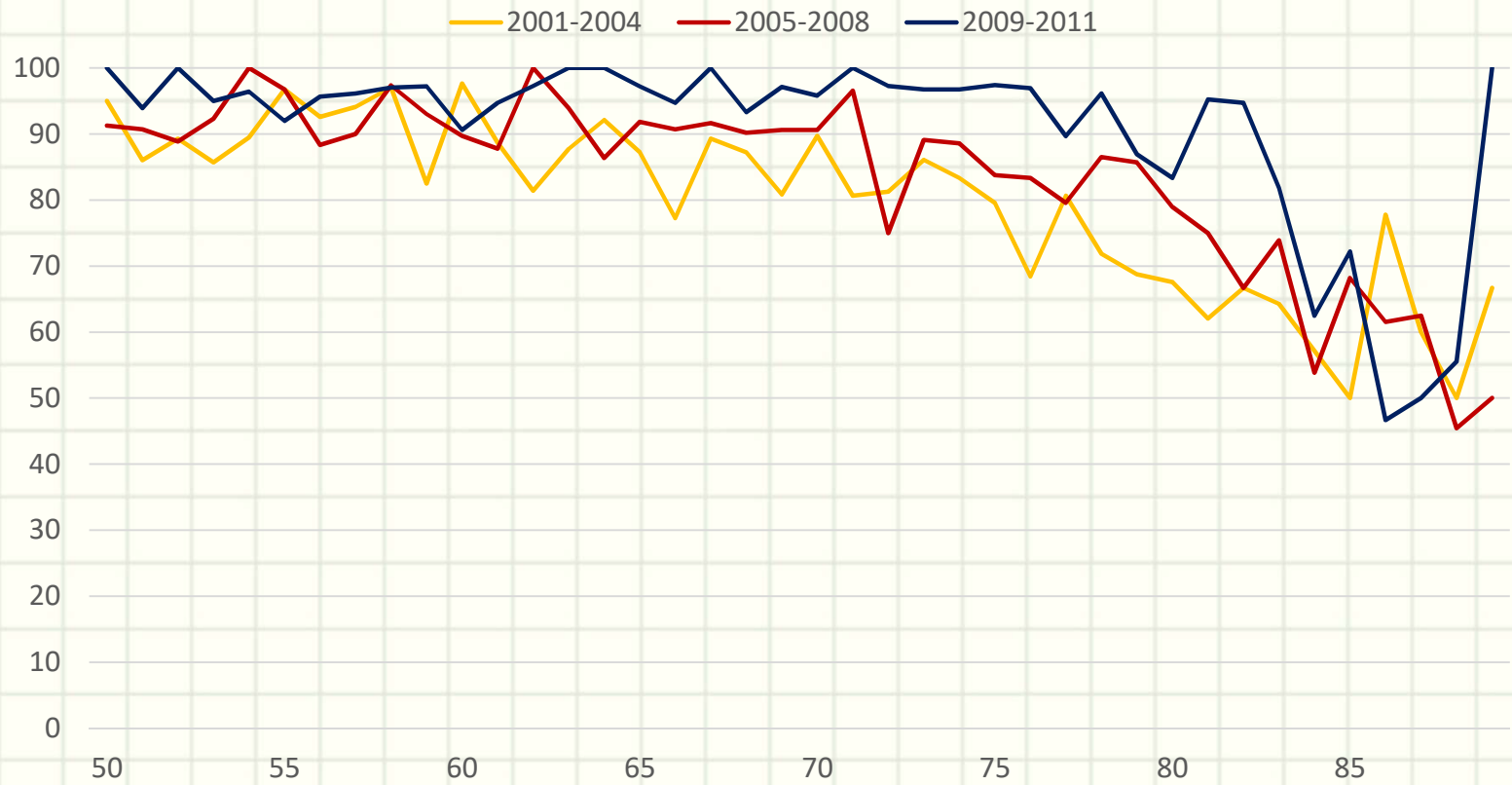


Percorso terapeutico post-BCS Rec+ per classi d'età

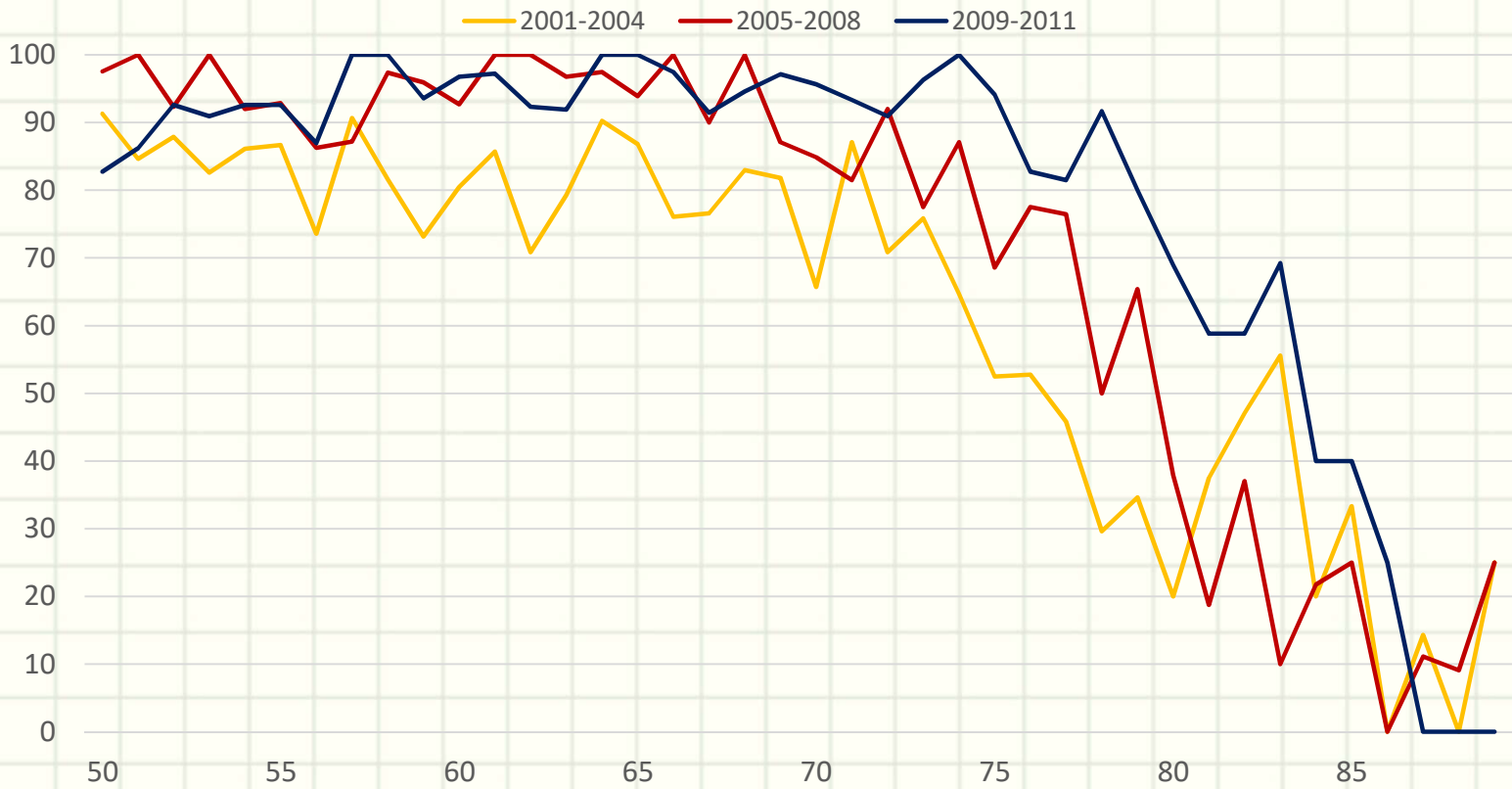


	50-59		60-69		70-79		80-89		Totale	
	n	% column	n	% column	n	% column	n	% column	n	% column
BCS	14	1,69	21	2,02	48	6,72	87	27,27	170	5,85
BCS + OT	70	8,43	81	7,78	111	15,55	126	39,50	388	13,36
BCS + RT	37	4,46	73	7,01	34	4,76	10	3,13	154	5,30
BCS + OT+ RT	709	85,42	866	83,19	521	72,97	96	30,10	2192	75,49
Totale	**830**	100,00	**1041**	100,00	**714**	100,00	**319**	100,00	**2904**	100,00

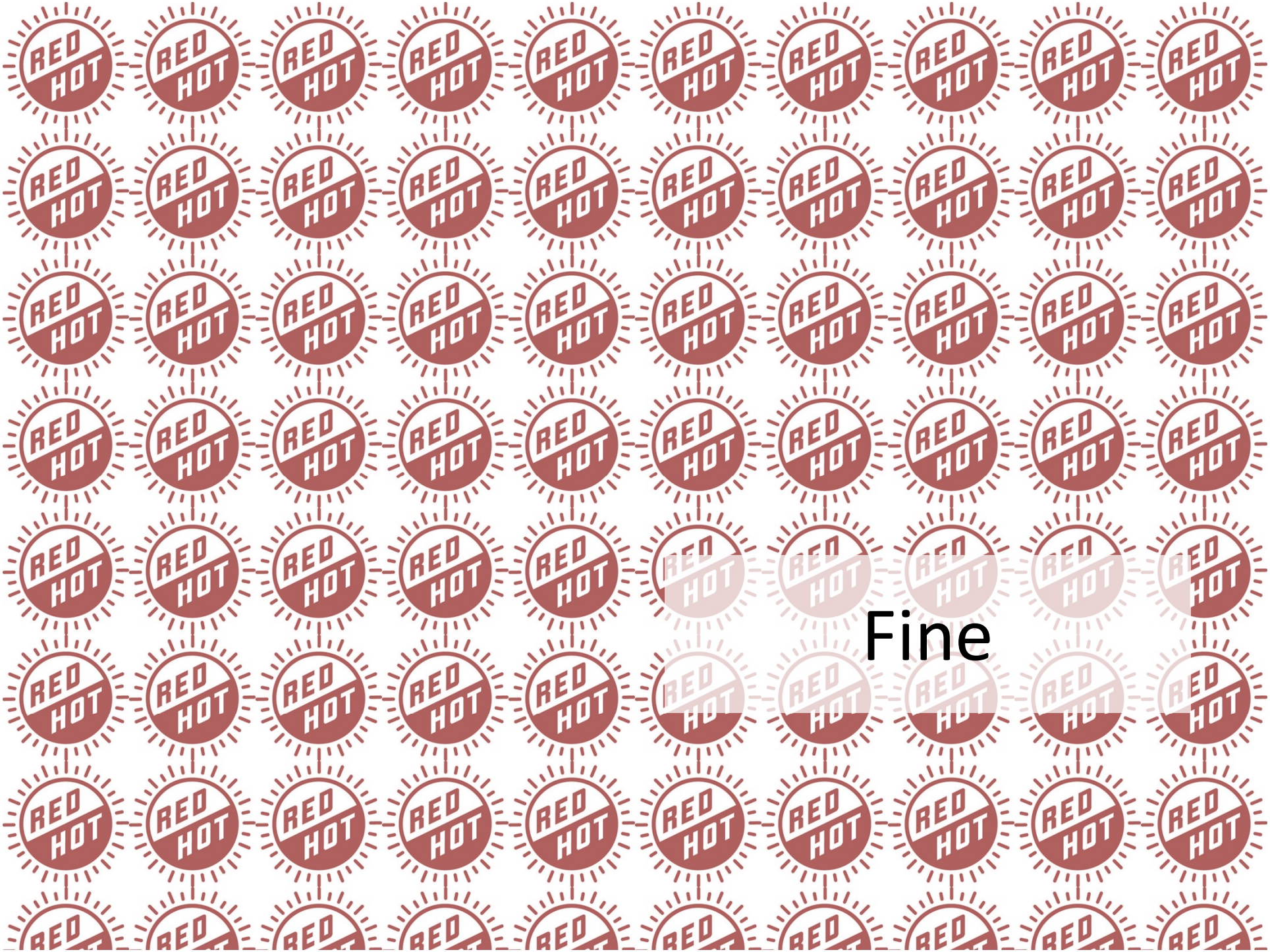
Ormonoterapia per età alla diagnosi e periodo



Radioterapia per età alla diagnosi e periodo



Chemioterapia per età alla diagnosi e periodo


Fine