Evidence to Support Screening

Edward A. Sickles, MD

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Types of Evidence Supporting Screening

- Randomized controlled trials
- Case-control studies
- Incidence-based mortality studies
- Trend studies
- Expert opinion
- Anecdotal reports

Data limited to randomized controlled trials involves screening only with mammography, only at ages 40-69, and only for average-risk women.

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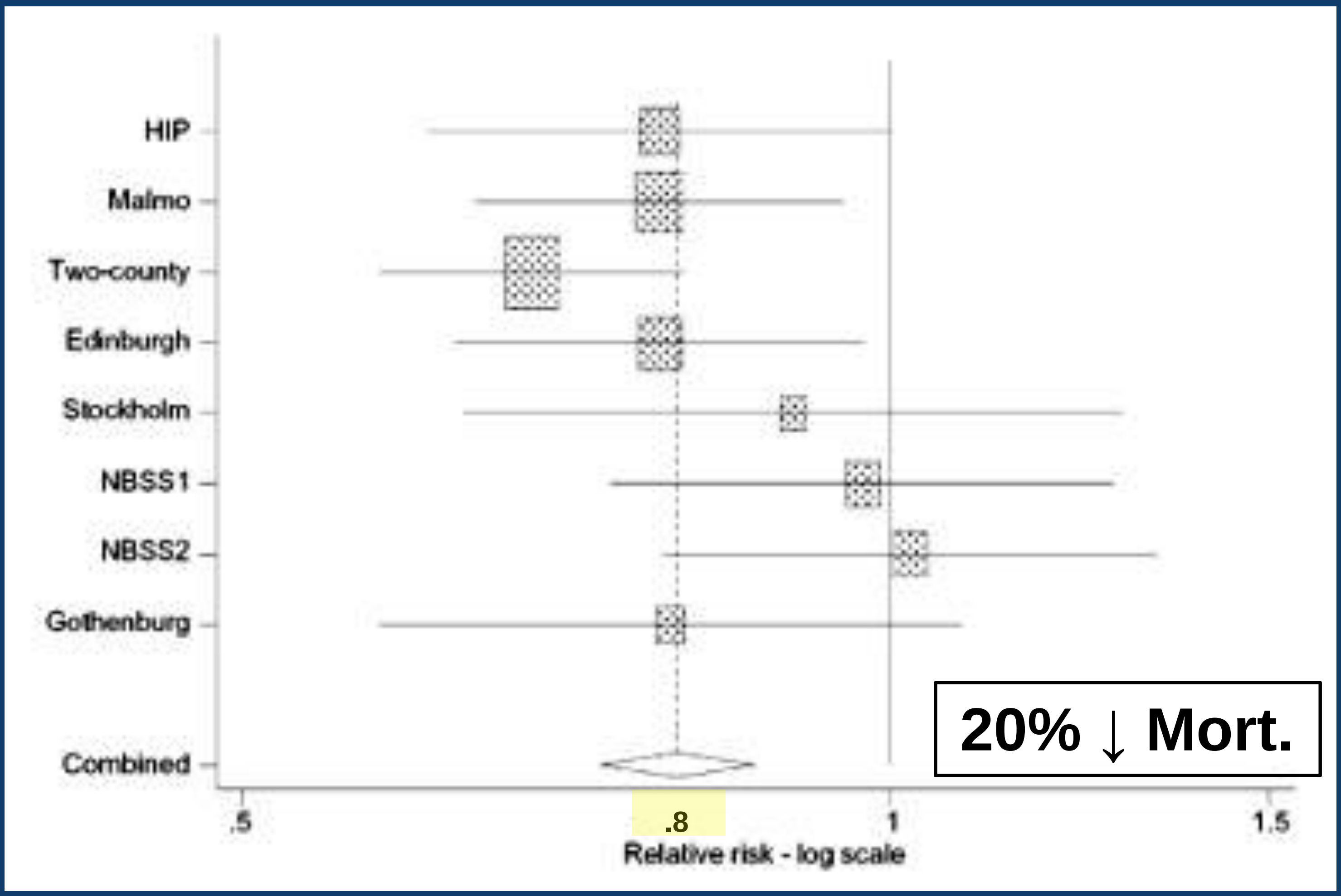
RCT Evidence (Ages 40-69)



Relative risk = 0.80 (0.73-0.86)

Radiol Clin North Am 2004; 42:793-806

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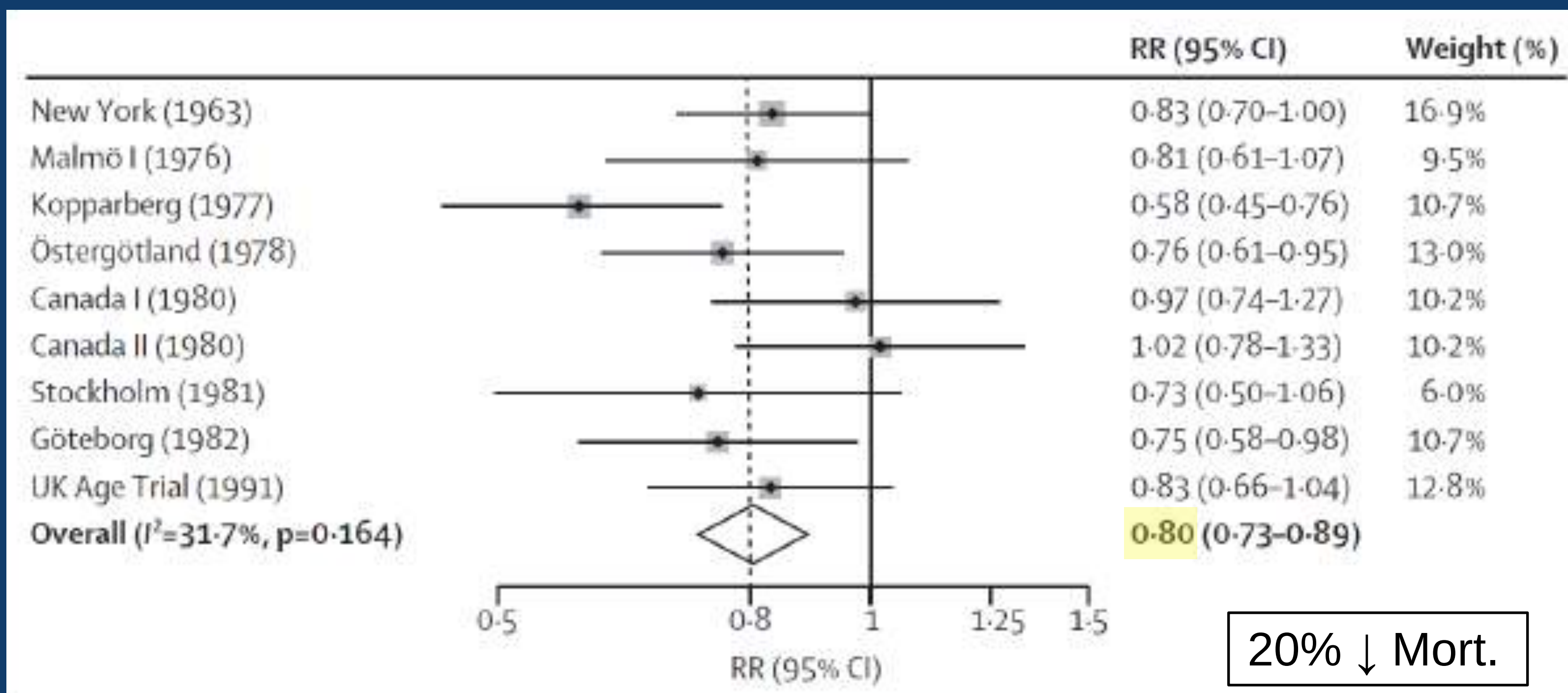
RCT Evidence (Ages 40-69)



Relative risk = 0.79 (0.73-0.86)

Breast Cancer Management 2012; 1:31-38

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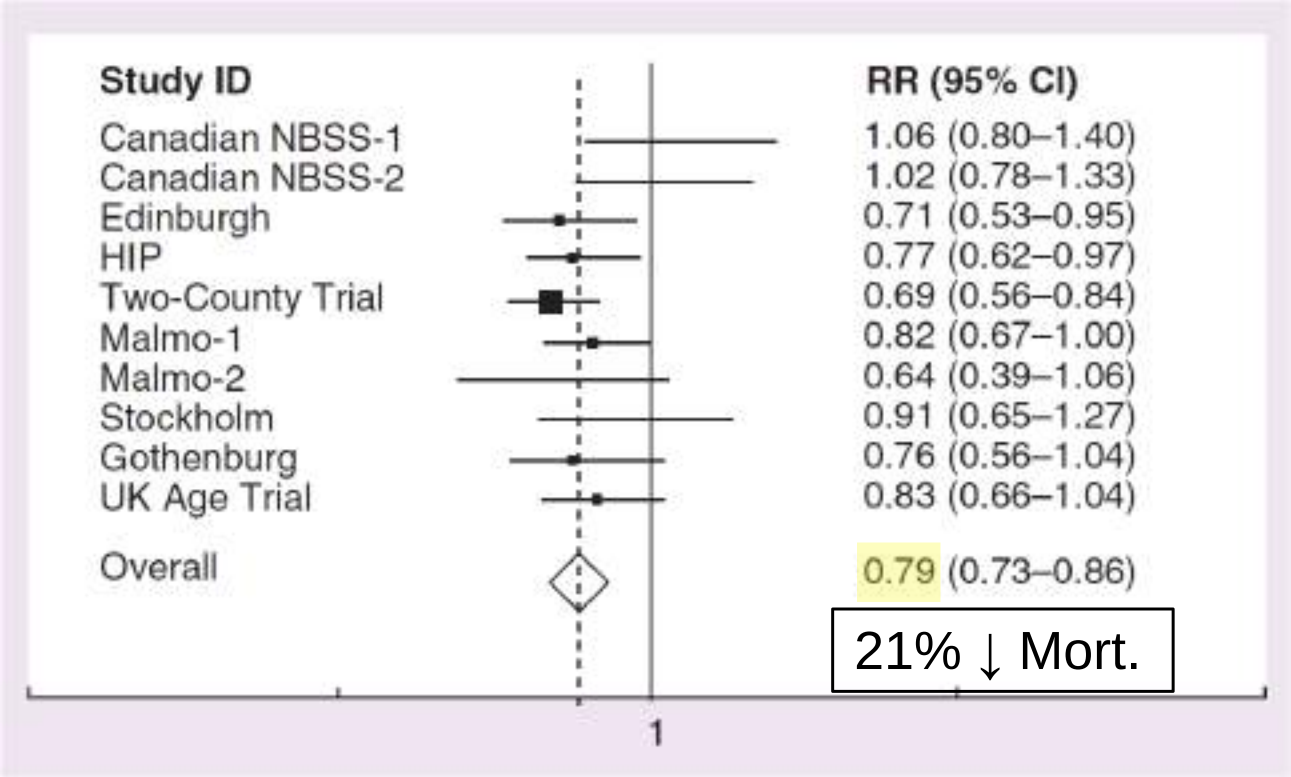
RCT Evidence (Ages 40-69)



Relative risk = 0.80 (0.73-0.86)

Lancet 2012; 380:1778-1786

RCT Evidence (Ages 40-69)

- Scientific rigor of RCT experimental design is necessary to establish the benefit of mortality reduction
- Magnitude of observed benefit in RCTs is likely to underestimate the actual benefit achieved in the clinical practice setting

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Why Do RCTs Underestimate Benefit?

- Non-compliance in the cohort invited to screening
- Contamination in the cohort not invited to screening

Why Else Do RCTs Underestimate Benefit?

Screening intervals too long

Too few screening rounds

Follow-up times too short

One versus two mammographic views

Suboptimal mammographic technique

Recall rates too low

Types of Evidence Supporting Screening

Randomized controlled trials

Case-control studies

Incidence-based mortality studies

Trend studies

Expert opinion

Anecdotal reports

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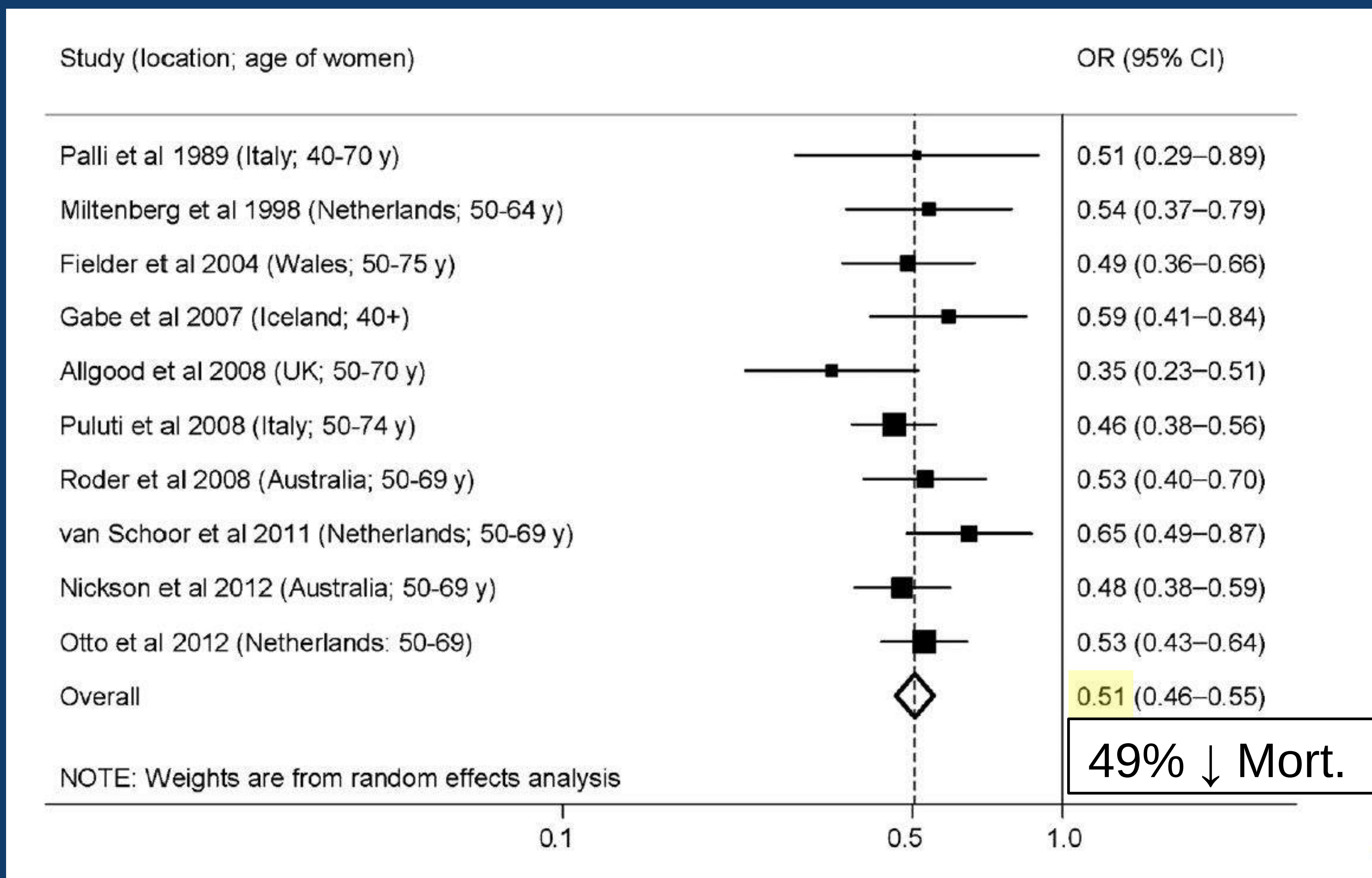
Case-Control Studies (Ages 40-75)

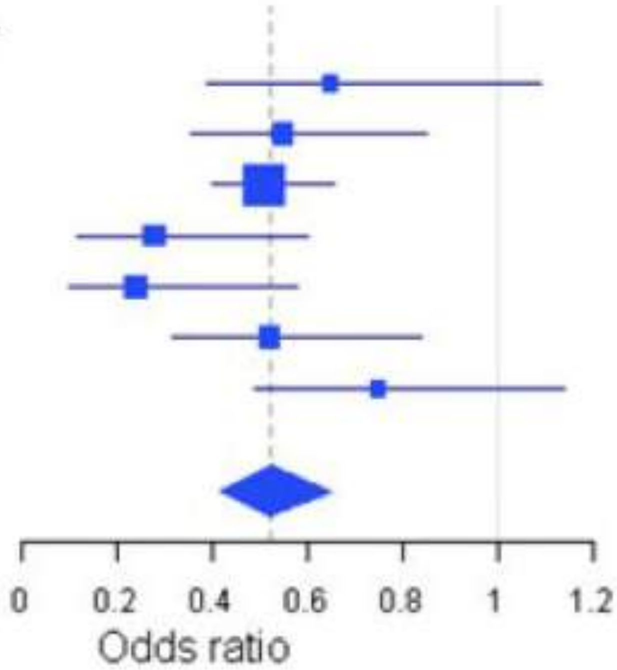


Cancer Epidemiol Biomarkers Prev 2012; 21:1479-1488

Case-Control Studies (Ages 40-75)

Screened vs Unscreened

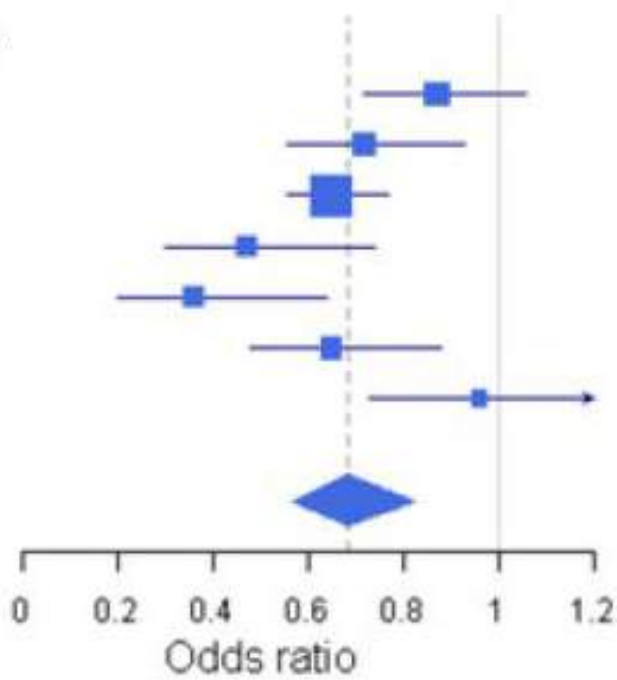
Study	OR	Lower	Upper
Gabe, (2007)[40]	0.65	0.39	1.09
Puliti, (2008)[43]	0.55	0.36	0.85
Otto, (2012)[47]	0.51	0.4	0.66
Van Schoor, (2011)[15]	0.28	0.12	0.6
Paap, (2010)[49]	0.24	0.1	0.58
Allgood, (2008)[65]	0.52	0.32	0.84
Fielder, (2004)[66]	0.75	0.49	1.14
Summary (random)	**0.52**	**0.42**	**0.65**



48% ↓ Mort.

Invited vs Not Invited

Study	OR	Lower	Upper
Gabe, (2007)[40]	0.87	0.72	1.06
Puliti, (2008)[43]	0.72	0.56	0.93
Otto, (2012)[47]	0.65	0.56	0.77
Van Schoor, (2011)[15]	0.47	0.3	0.74
Paap, (2010)[49]	0.36	0.2	0.64
Allgood, (2008)[65]	0.65	0.48	0.88
Fielder, (2004)[66]	0.96	0.73	1.27
Summary (random)	**0.69**	**0.57**	**0.83**



31% ↓ Mort.

J Med Screen 2012; 19 Suppl 1:14-25

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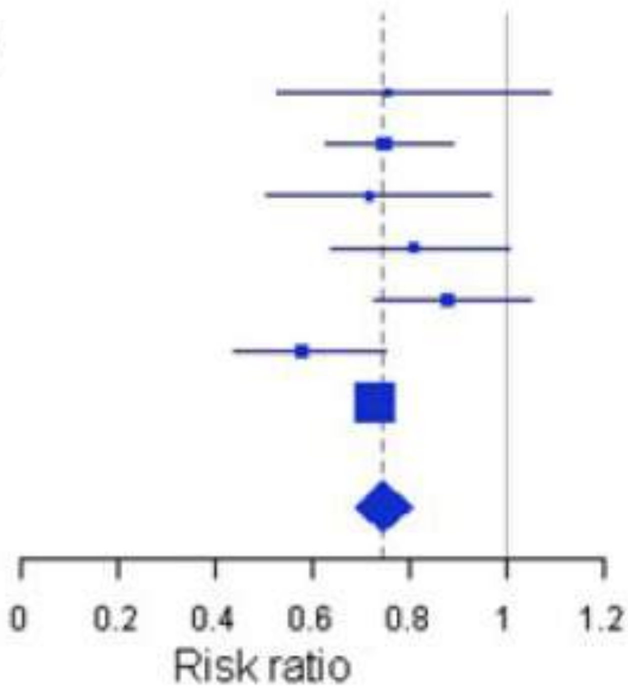
Europe Service Screening

Invited vs Not Invited

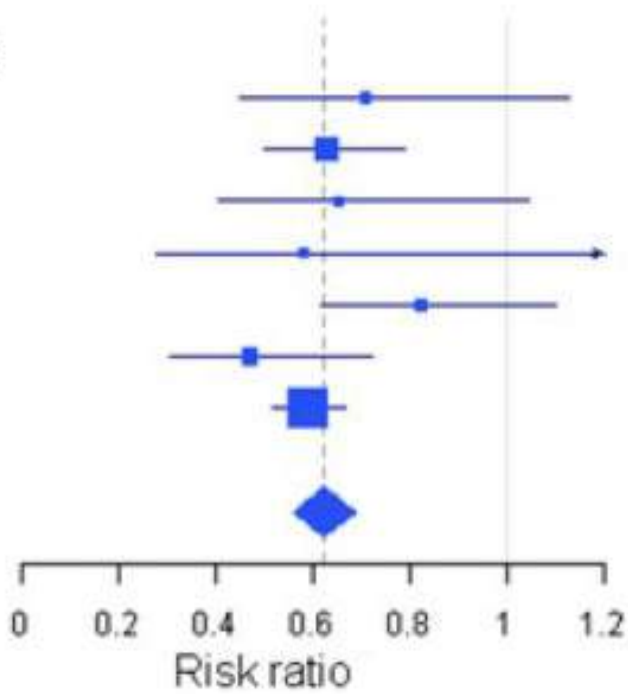
Study	RR	Lower	Upper
Hakama, (1997)[39]	0.76	0.53	1.09
Olsen, (2005)[32]	0.75	0.63	0.89
Sarkeala, (2008)[36]	0.72	0.51	0.97
Paci, (2002)[42]	0.81	0.64	1.01
Kalager, (2010)[51]	0.88	0.73	1.05
Ascunce, (2007)[53]	0.58	0.44	0.75
SOSSEG, (2006)[59]	0.73	0.69	0.77
Summary (random)	**0.75**	**0.69**	**0.81**



25% ↓ Mort.

Screened vs Unscreened

Study	RR	Lower	Upper
Hakama, (1997)[39]	0.71	0.45	1.13
Olsen, (2005)[32]	0.63	0.5	0.79
Sarkeala, (2008)[36]	0.65	0.41	1.05
Paci, (2002)[42]	0.58	0.28	1.22
Kalager, (2010)[51]	0.82	0.62	1.1
Ascunce, (2007)[53]	0.47	0.31	0.73
SOSSEG, (2006)[59]	0.59	0.52	0.67
Summary (random)	**0.62**	**0.56**	**0.69**



38% ↓ Mort.

J Med Screen 2012; 19 Suppl 1:14-25

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Intention-to-Screen vs. Actually Screened

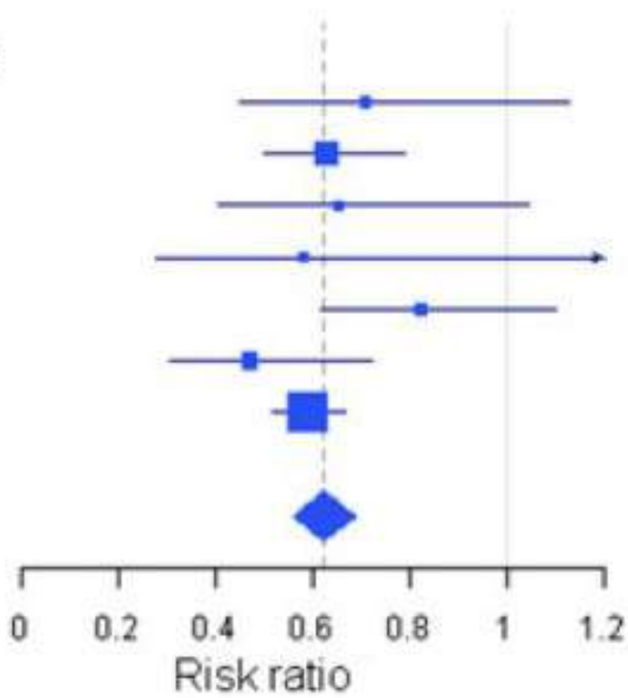
- Intention-to-screen takes the societal perspective, of special interest to those who must plan and pay for screening (insurers, policy planners, governments)
- Actually screened reflects clinical practice, taking the individual woman's (patient's) perspective

Europe Service Screening (Ages 50-74)

Screened vs Unscreened

Study	RR	Lower	Upper
Hakama, (1997)[39]	0.71	0.45	1.13
Olsen, (2005)[32]	0.63	0.5	0.79
Sarkeala, (2008)[36]	0.65	0.41	1.05
Paci, (2002)[42]	0.58	0.28	1.22
Kalager, (2010)[51]	0.82	0.62	1.1
Ascunce, (2007)[53]	0.47	0.31	0.73
SOSSEG, (2006)[59]	0.59	0.52	0.67
Summary (random)	**0.62**	**0.56**	**0.69**

38% ↓ Mort.



J Med Screen 2012; 19 Suppl 1:14-25

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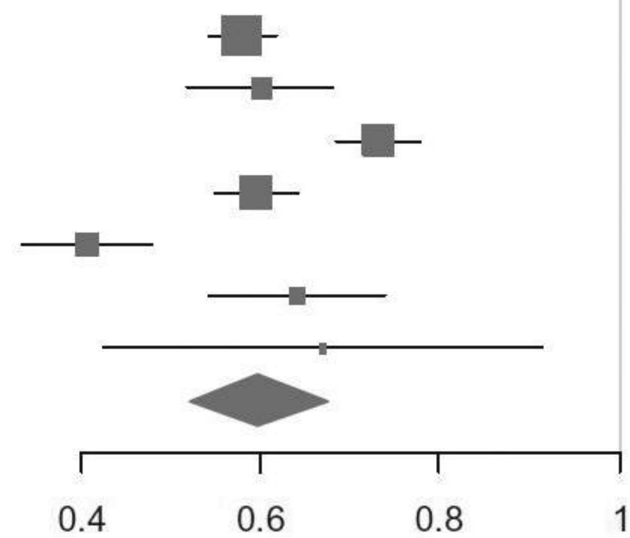
Canada Service Screening (Ages 40-79)

Region	SMR	95% CI
British Columbia	0.58	0.54 to 0.62
Manitoba	0.60	0.52 to 0.68
Ontario	0.73	0.68 to 0.78
Quebec	0.59	0.55 to 0.64
New Brunswick	0.41	0.33 to 0.48
Nova Scotia	0.64	0.54 to 0.74
Newfoundland and Labrador	0.67	0.42 to 0.91
Summary (random)	**0.60**	**0.52 to 0.67**

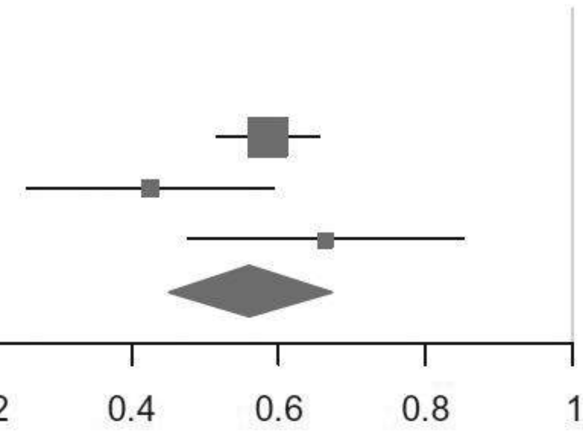
40% ↓ Mort.



J Natl Cancer Inst 2014; 106(11):dju261 dci:10.1093/jnci/dju261

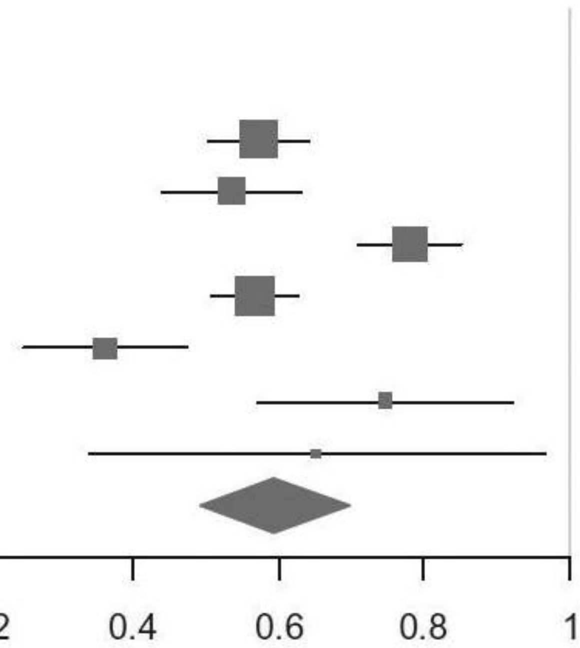
Canada Service Screening
(Ages 40-49, 50-59)

Region	SMR	95% CI
British Columbia	0.58	0.51 to 0.65
New Brunswick	0.42	0.26 to 0.59
Nova Scotia	0.66	0.47 to 0.85
Summary (random)	**0.56**	**0.45 to 0.67**



Ages 40-49: 44% ↓ Mort.

Region	SMR	95% CI
British Columbia	0.57	0.51 to 0.64
Manitoba	0.54	0.44 to 0.63
Ontario	0.78	0.71 to 0.85
Quebec	0.57	0.51 to 0.63
New Brunswick	0.37	0.25 to 0.48
Nova Scotia	0.75	0.57 to 0.92
Newfoundland and Labrador	0.65	0.34 to 0.97
Summary (random)	**0.60**	**0.49 to 0.70**



Ages 50-59: 40% ↓ Mort.

J Natl Cancer Inst 2014; 106(11):dju261 dci:10.1093/jnci/dju261

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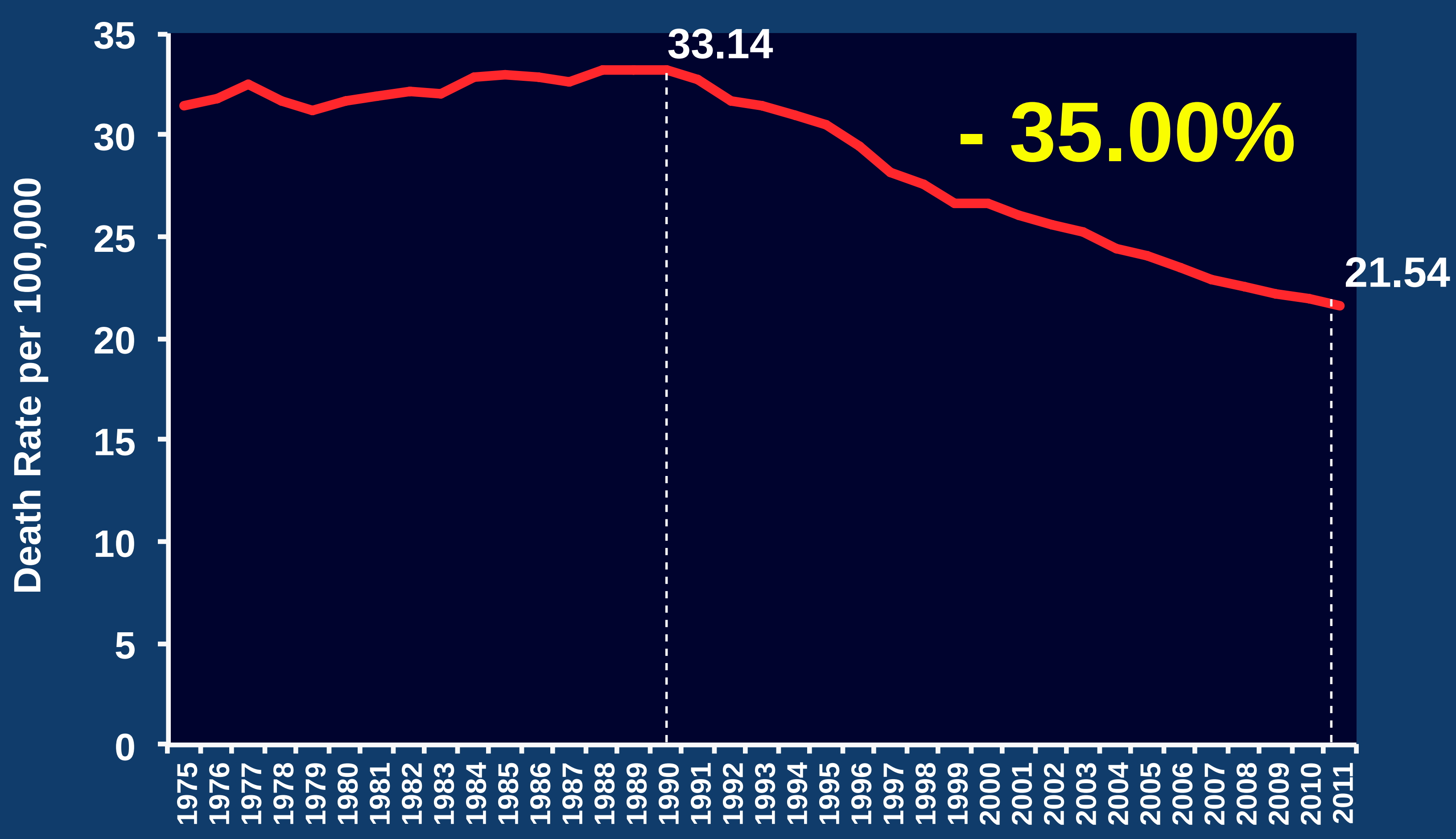
Reliable service screening data are not available from the United States because, for a variety of reasons, here screening is provided ad hoc (opportunistic) rather than within centrally organized population-based screening programs.

In the USA, we also have no national tumor registry to permit tracking of outcomes among all women, or among screened versus unscreened women.

Age-Adjusted U.S. Death Rate – Female Breast Cancer (Invasive)

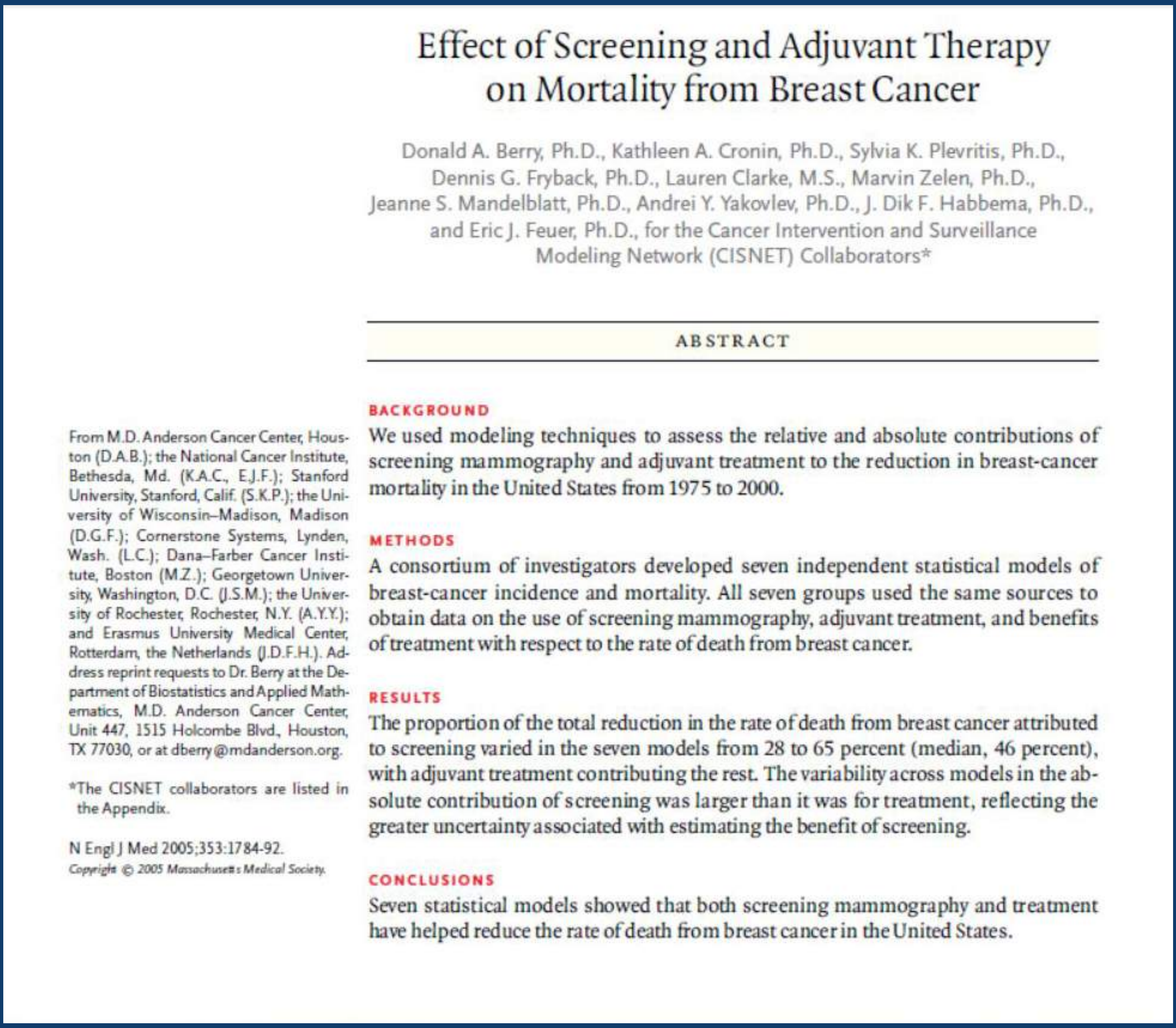


SEER Cancer Statistics Review 1975-2011 *(http://seer.cancer.gov/csr/)*

Causes of BC Mortality Reduction

Screening (early BC detection)

Improved BC treatment



Effect of Screening and Adjuvant Therapy on Mortality from Breast Cancer

Donald A. Berry, Ph.D., Kathleen A. Cronin, Ph.D., Sylvia K. Plevritis, Ph.D., Dennis G. Fryback, Ph.D., Lauren Clarke, M.S., Marvin Zelen, Ph.D., Jeanne S. Mandelblatt, Ph.D., Andrei Y. Yakovlev, Ph.D., J. Dik F. Habbema, Ph.D., and Eric J. Feuer, Ph.D., for the Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators*

ABSTRACT

BACKGROUND

We used modeling techniques to assess the relative and absolute contributions of screening mammography and adjuvant treatment to the reduction in breast-cancer mortality in the United States from 1975 to 2000.

METHODS

A consortium of investigators developed seven independent statistical models of breast-cancer incidence and mortality. All seven groups used the same sources to obtain data on the use of screening mammography, adjuvant treatment, and benefits of treatment with respect to the rate of death from breast cancer.

RESULTS

The proportion of the total reduction in the rate of death from breast cancer attributed to screening varied in the seven models from 28 to 65 percent (median, 46 percent), with adjuvant treatment contributing the rest. The variability across models in the absolute contribution of screening was larger than it was for treatment, reflecting the greater uncertainty associated with estimating the benefit of screening.

CONCLUSIONS

Seven statistical models showed that both screening mammography and treatment have helped reduce the rate of death from breast cancer in the United States.

From M.D. Anderson Cancer Center, Houston (D.A.B.); the National Cancer Institute, Bethesda, Md. (K.A.C., E.J.F.); Stanford University, Stanford, Calif. (S.K.P.); the University of Wisconsin–Madison, Madison (D.G.F.); Cornerstone Systems, Lynden, Wash. (L.C.); Dana–Farber Cancer Institute, Boston (M.Z.); Georgetown University, Washington, D.C. (J.S.M.); the University of Rochester, Rochester, N.Y. (A.Y.Y.); and Erasmus University Medical Center, Rotterdam, the Netherlands (J.D.F.H.). Address reprint requests to Dr. Berry at the Department of Biostatistics and Applied Mathematics, M.D. Anderson Cancer Center, Unit 447, 1515 Holcombe Blvd., Houston, TX 77030, or at dberry@mdanderson.org.

*The CISNET collaborators are listed in the Appendix.

N Engl J Med 2005;353:1784-92.

N Engl J Med 2005; 353:1784-1792

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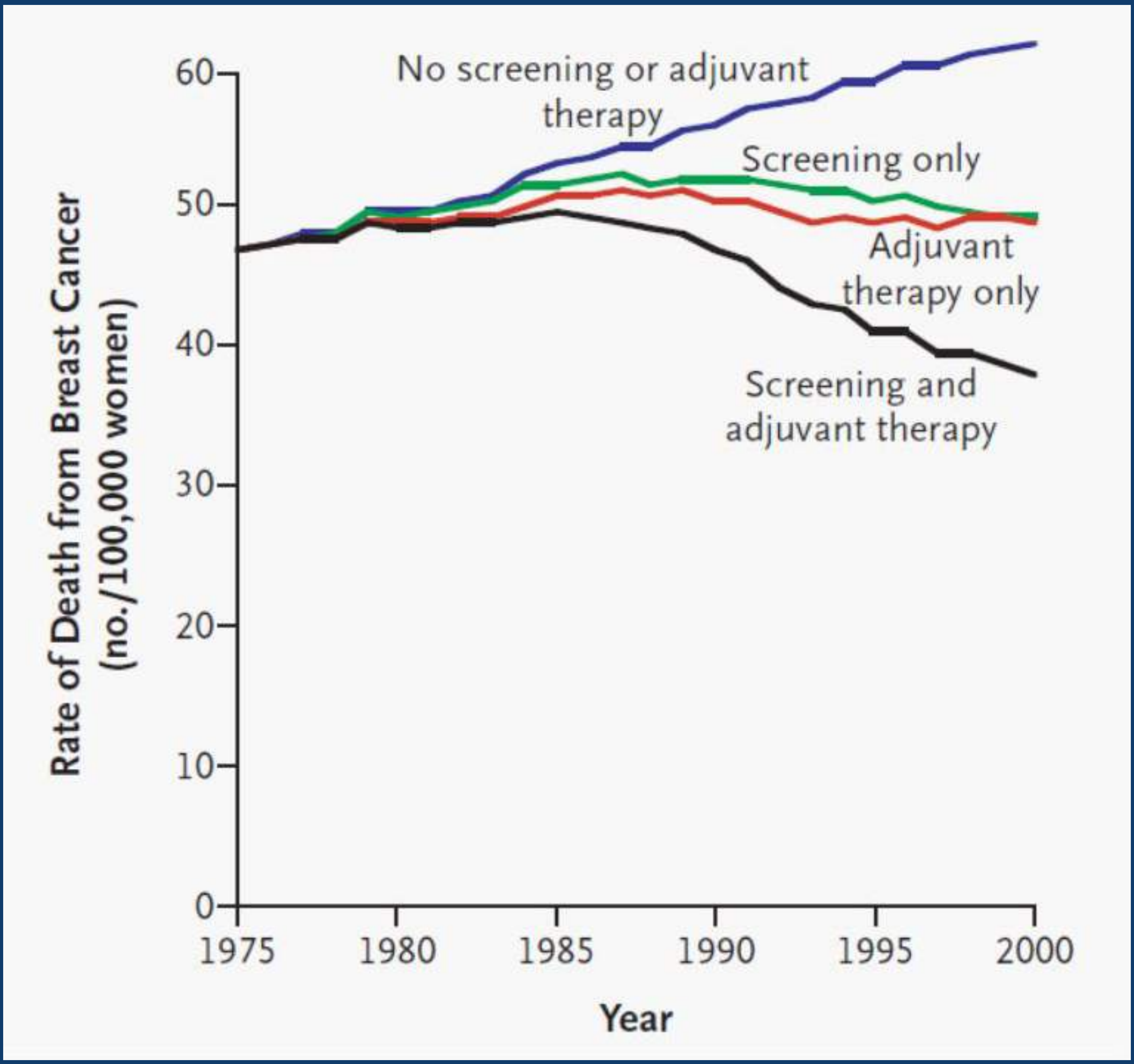
Causes of BC Mortality Reduction



N Engl J Med 2005; 353:1784-1792

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Service Screening in Sweden

Some counties offered screening to women ages 40-49, other counties did not

Natural experiment: breast cancer care in all counties was otherwise the same

Larger age 40-49 population studied than all RCTs combined (16 million person-years)

26% mortality reduction for women living in screening (invited) vs non-screening counties, mean follow-up 16 years

Cancer 2011; 117:714-722

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Estimates of Advanced Cancer Frequency

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence

Archie Bleyer, M.D., and H. Gilbert Welch, M.D., M.P.H.

ABSTRACT

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.

N Engl J Med 2005; 353:1784-1792

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Estimates of Advanced Cancer Frequency

Reduction in Late-Stage Breast Cancer Incidence in the Mammography Era

Implications for Overdiagnosis of Invasive Cancer

Mark A. Helvie, MD[1]; Joanne T. Chang, MPH[2]; R. Edward Hendrick, PhD[3]; and Mousumi Banerjee, PhD[4]

BACKGROUND: Mammographic screening is expected to decrease the incidence of late-stage breast cancer. In the current study, the authors determined the decrease in late-stage cancer incidence and the changes in invasive cancer incidence that occurred in the mammographic era after adjusting for prescreening temporal trends. **METHODS:** Breast cancer incidence and stage data were obtained from the Surveillance, Epidemiology, and End Results program. The premammography period (1977-1979) was compared with the mammographic screening period (2007-2009) for women aged ≥ 40 years. The authors estimated prescreening temporal trends using 5 measures of annual percentage change (APC). Stage-specific incidence values from 1977 through 1979 (baseline) were adjusted using APC values of 0.5%, 1.0%, 1.3%, and 2.0% and then compared with observed stage-specific incidence in 2007 through 2009. **RESULTS:** Prescreening APC temporal trend estimates ranged from 0.8% to 2.3%. The joinpoint estimate of 1.3% for women aged ≥ 40 years approximated the 4-decade long APC trend of 1.2% noted in the Connecticut Tumor Registry. At an APC of 1.3%, late-stage breast cancer incidence decreased by 37% (56 cases per 100,000 women) with a reciprocal increase in early-stage rates noted from 1977 through 1979 to 2007 through 2009. Resulting late-stage cancer incidence decreased from 21% at an APC of 0.5% to 48% at an APC of 2.0%. Total invasive breast cancer incidence decreased by 9% (27 cases per 100,000 women) at an APC of 1.3%. **CONCLUSIONS:** There is evidence that a substantial reduction in late-stage breast cancer has occurred in the mammography era when appropriate adjustments are made for prescreening temporal trends. At background APC estimates of ≥ 1%, the total invasive breast cancer incidence also decreased. *Cancer* **2014;120:2649-56.** © *2014 American Cancer Society.*

KEYWORDS: mammography, screening, overdiagnosis, breast cancer, late-stage disease.

- 37%

Cancer 2014; 120:2649-2656

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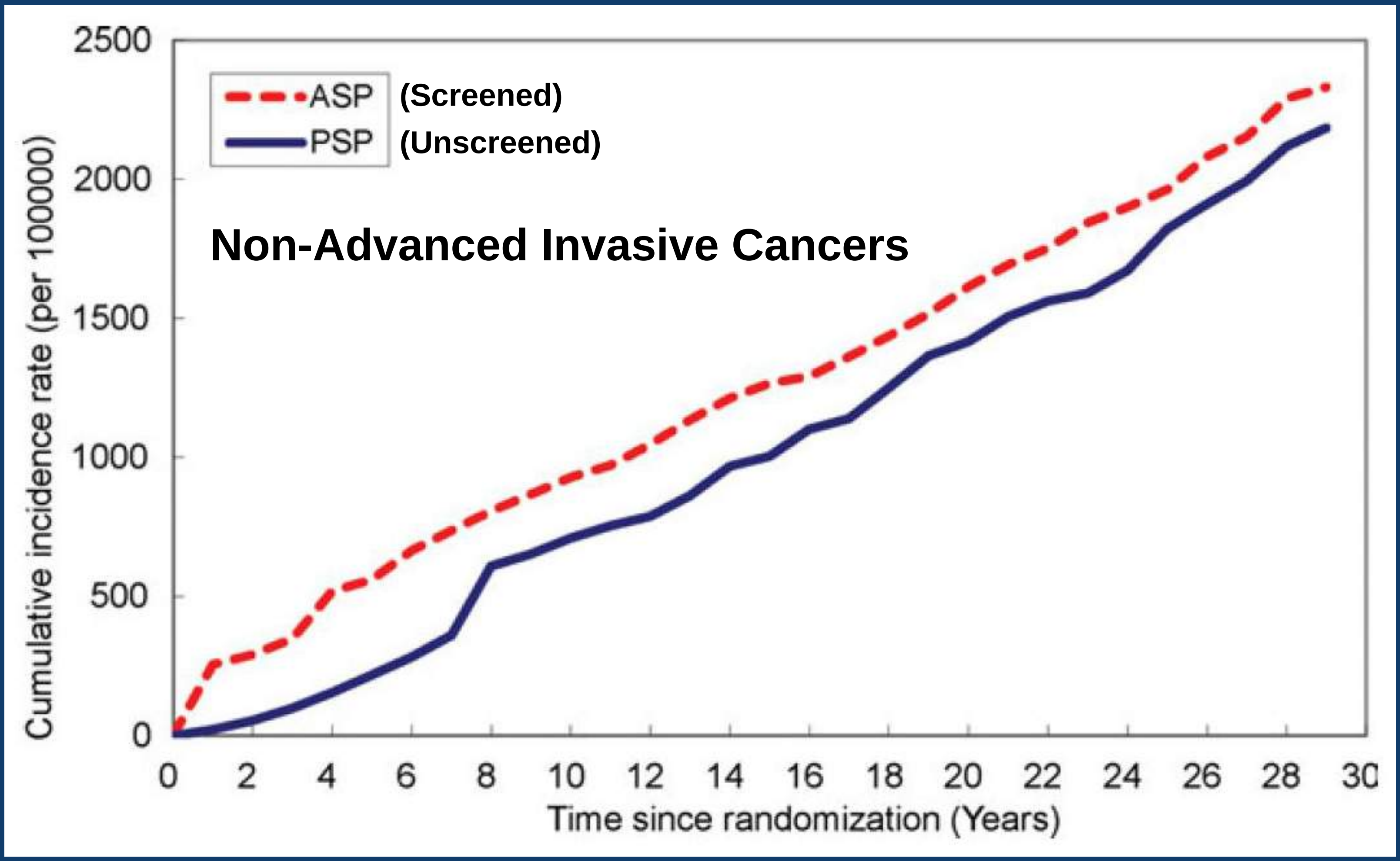
Non-Advanced Invasive Cancer Frequency



Cancer 2012; 118:5728-5732

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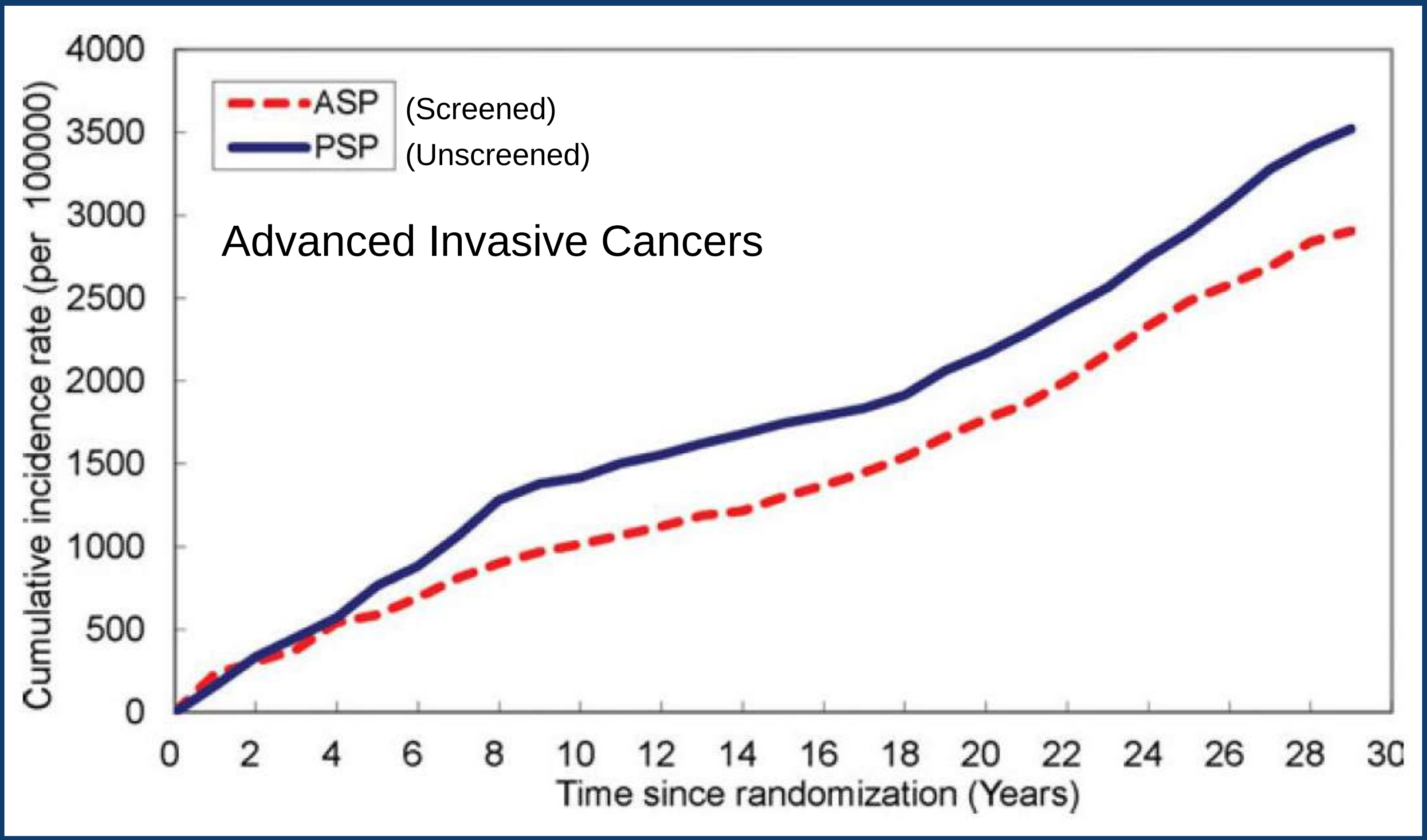
Advanced Invasive Cancer Frequency



Cancer 2012; 118:5728-5732

Advanced Invasive Cancer Frequency

Insights from the Breast Cancer Screening Trials: How Screening Affects the Natural History of Breast Cancer and Implications for Evaluating Service Screening Programs

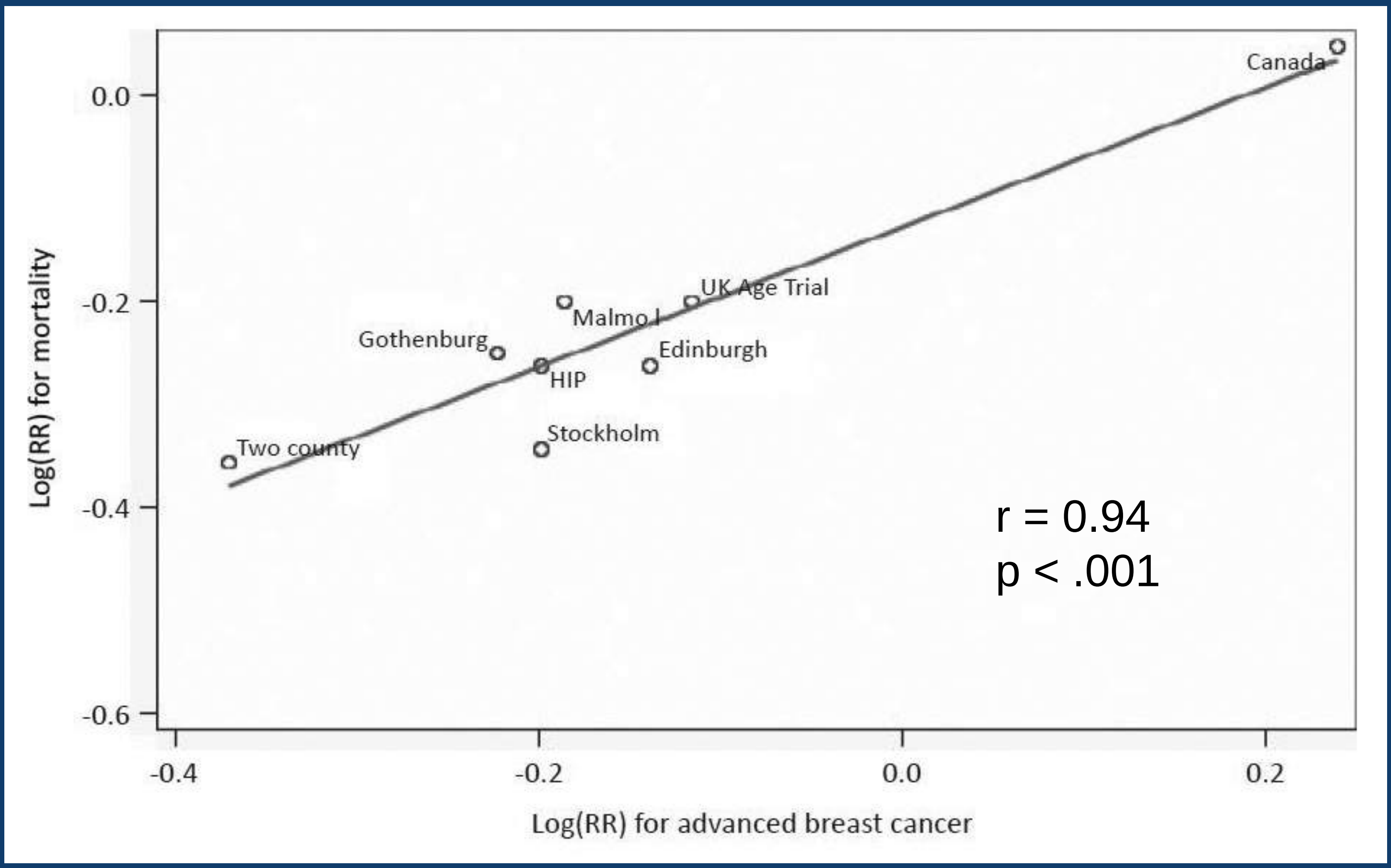
László Tabár, MD,* Amy Ming-Fang Yen, PhD,† Wendy Yi-Ying Wu, PhD,‡ Sam Li-Sheng Chen, PhD,† Sherry Yueh-Hsia Chiu, PhD,§ Jean Ching-Yuan Fann, PhD,¶ May Mei-Sheng Ku, PhD,‡ Robert A Smith, PhD,** Stephen W Duffy, MSc,†† and Tony Hsiu-Hsi Chen, PhD‡

**Department of Mammography, Central Hospital, Falun, Sweden; †School of Oral Hygiene, Taipei Medical University, Taipei, Taiwan; ‡Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; §Department and Graduate Institute of Health Care Management, Chang Gung University, Taoyuan, Taiwan; ¶Department of Health Industry Management, College of Healthcare Management, Kainan University, Taoyuan, Taiwan; **American Cancer Society, Atlanta, Georgia; ††Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK*

■ **Abstract:** It is desirable to have a strategy for evaluation of breast cancer service screening programs years before the long-term breast cancer mortality data are available. Since successful mammography screening has a significant impact on two components of the TNM (tumor size, node status, presence or absence of distant metastases) classification system, tumor size and node status, we investigated the effect of the randomized breast screening trials on incidence of advanced stage disease and on the subsequent breast cancer death rate. In the trials that achieved a 20% or greater reduction in advanced stage disease, there was an average breast cancer mortality reduction of 28% among women invited to screening (attenders and nonattenders combined). In the trials that achieved a reduction in advanced stage disease of less than 10%, there was no reduction in breast cancer mortality among women invited to screening. This study provides evidence that the average mortality reduction in all the trials underestimates the true mortality reduction, and that substantially greater breast cancer mortality reductions can be expected in screening programs that are effective in reducing advanced stage breast cancer. In addition, monitoring the incidence of advanced stage breast cancer in an ongoing screening program can provide a sensitive and early indicator of the subsequent mortality from the disease. ■

Breast J 2015; 21(1):1-8

Advanced Invasive Cancer Frequency



Breast J 2015; 21(1):1-8

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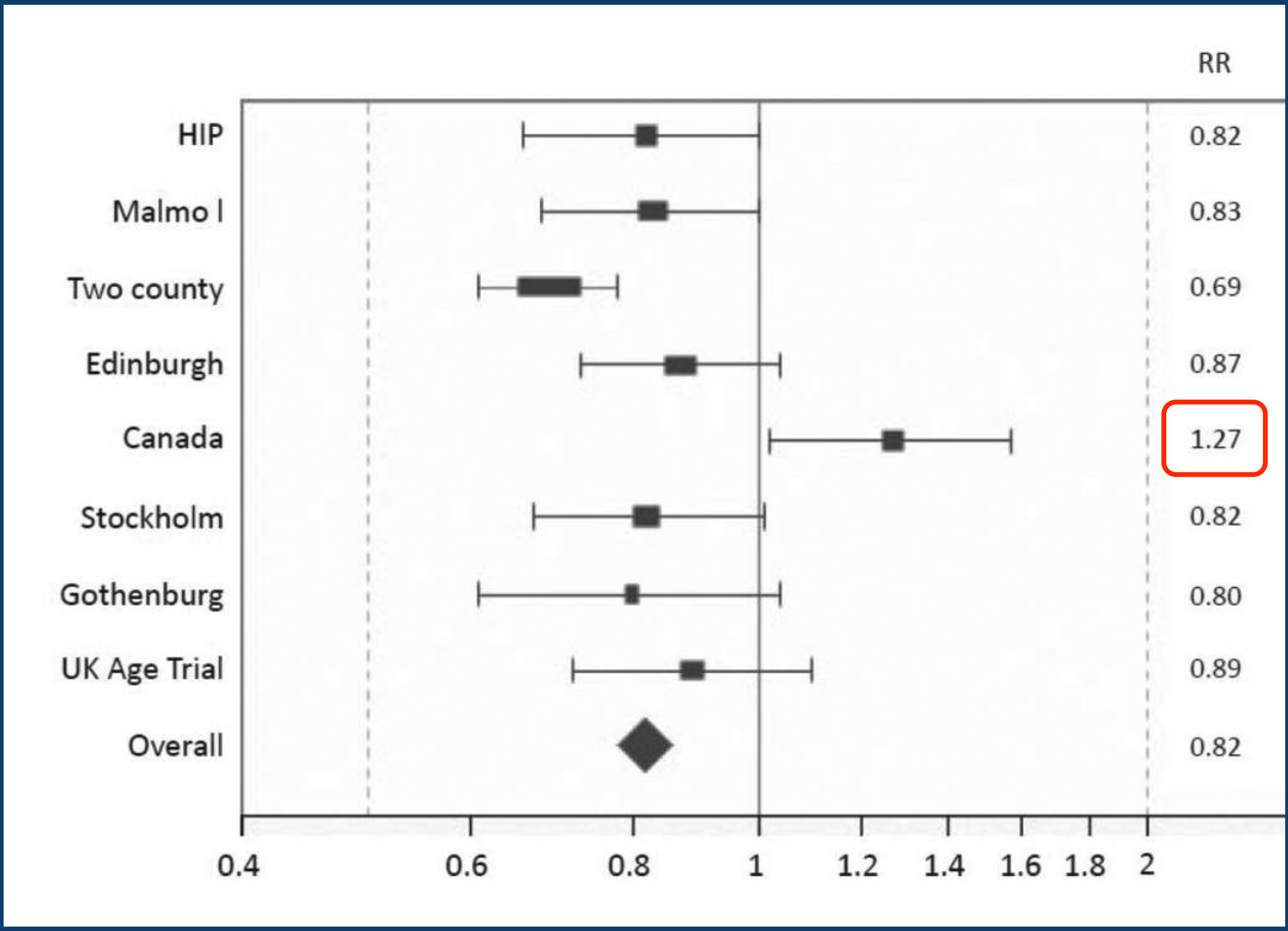
Advanced Invasive Cancer Frequency



Breast J 2015; 21(1):1-8

Benefits of Mammography Screening

Mortality reduction

Less morbidity from cancer treatment

- Less extensive surgery
- Less frequent chemotherapy
- Less aggressive chemotherapy

Less Morbidity from Cancer Treatment

Studies in USA, Canada, Europe, Australia

Am Surg 1999; 65(11):1061-1066

ANZ J Surg 2001; 71(7):398-402

AJR Am J Roentgenol 2005; 184(1):324-329

Brit J Cancer 2006; 95(9):1265-1268

Int J Cancer 2007; 120(10):2185-2190

Radiology 2012; 262(3):797-806

Radiology 2014; 273(3):686-694

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Less Morbidity from Cancer Treatment

	Ages	Surgery	ChemoRx
Am Surg	40-49	✓	
ANZ J Surg	50-69	✓	
AJR	All		✓
Brit J Cancer	All	✓	
Int J Cancer	All	✓	✓
Radiol 2012	40-49	✓	✓
Radiol 2014	≥75	✓	✓

Benefits of Mammography Screening

Mortality reduction

Less morbidity from cancer treatment

- Less extensive surgery
- Less frequent chemotherapy
- Less aggressive chemotherapy

Reduced anxiety (true-negatives)

Reduced anxiety (earlier diagnosis)

Identify high-risk lesions for Dx / Rx