

# Screening Controversies 2014: The Best of Times and The Worst of Times

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# This is the Best of Times for Screening Mammography

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- Proof of substantial benefit from screening mammography has never been more incontrovertible
  - Alleged risks from screening have all been scientifically debunked
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# This is also the Worst of Times for Screening Mammography

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Myths of little or no benefit and  
wildly overstated harms:

- Are widely believed by the under informed
- And stridently propagated by some pseudoacademics, who should know better

# Demonstrated Benefits From Screening Mammography

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- Swedish Two-County Randomized Trial:  
31% mortality reduction for ages 40 - 74
- Swedish 7 County Service Screening Study  
45% mortality reduction in screenees

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## Summary Results from 7 European Incidence-Based Mortality Service Screening Studies

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	Mortality Reduction
Invited vs Not Invited	25%
Screened vs Not Screened	38%

Broeders et al. J Med Screening 2012

# Summary Results from 7 European Case-Control Service Screening Studies

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	Mortality Reduction
Invited vs Not Invited	31%
Screened vs Not Screened	52%

Broeders et al. J Med Screening 2012

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## Why Do All Screening Studies Underestimate Benefits Why Do All

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- Screening intervals too long
- Trial length too short
- One vs. two mammographic views
- Older mammo techniques / equipment
- Avoidable errors in interpretation:
  - Missed cancers
  - Recall / biopsy rates too low

# American Cancer Society Screening Mammography Guidelines Studies

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- Women at average risk for breast cancer
  - Annual screening from age 40
  - No upper age to stop screening
    - older women unless their normal life expectancy is less than 5 years or
    - they have significant co-morbid condition

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## 2009 US Preventive Services Task Force Breast Cancer Screening Recommendations

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AGAINST	Routine screening mammography in women age 40-49
AGAINST	Teaching breast self examination
AGAINST	Clinical breast examination
AGAINST	Screening mammography in women age 75 and older
AGAINST	Annual screening mammography in women age 50-74
FOR	Only screening ages 50-74 every other year

# 2009 US Preventive Services Task Force Breast Cancer Screening Recommendations

Age	Number of Trials Included	Mortality Reduction
39-49 years	8	15%
50-59 years	6	14%
60-69 years	2	32%
70-74 years	1	0%

Nelson et al. *Ann Intern Med* 2009; 151:727-737

## Why Are USPSTF Data for Mortality Reductions in Screening Mammography Trials Too Low or Invalid

- Data for ages 39-49 and 50-59 include Canadian NBSS
- NBSS had fatally flawed methodology and inadequate mammographic technique
- Excluding NBSS results improves mortality reduction: 26% - 30% vs 15%
- Age 70-74 subgroup should not be separated since too few women

## **Fatal Deficiencies in Mammographic Quality at NBSS**

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- Poor film processing
  - Old equipment
  - Inadequate positioning
  - Often no mammographic grids
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## **Fatal Methodologic Flaws at NBSS (National Breast Screening Study of Canada)**

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- Was a volunteer trial and not a population-based trial
- Enriched with symptomatic patients, palpable masses and late stage cancers
- Clinical exam performed prior to assignment to study group or control group
- Excess of late stage cancers and cancer deaths in the mammography study group was a likely consequence

## Screening Women over Age 70

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- 40% of all new breast cancer cases
  - Sparse data from trials
  - Continuation of benefit expected
  - Substantial life expectancy
    - 15 years at age 70
    - 9 years at age 80
    - 5 years at age 90
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## Why is Screening Ages 40 – 49 Important?

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- “About 20% of women whose deaths are attributed to breast cancer were diagnosed in their forties.”

“About 40% of the years of life lost from breast cancer are associated with cases diagnosed between ages 40 and 49.”

Shapiro, Venet, Strax, Venet: Periodic Screening for Breast Cancer.  
Johns Hopkins University Press 1988, p. 12,13.

# Breast Cancer Mortality Reduction in Sweden, Screened vs. Non-Screened Women, 20 Years Before and After Introduction of Screening

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Age at Screening	Mortality Reduction
40 – 69	44%
40 – 49	48%

Tabar et al, Lancet 2003

**Although breast cancer incidence is age-dependent, the number of women needed to be screened (NNS) to detect one cancer or to save one life among those ages 40-49 is acceptably similar to that for screening women ages 50-59**

# Rationale for USPSTF Recommendation to Screen Every Other Year instead of Annually From Age 50-74 And No

	<u>Estimates from their Mathematical Models</u>	
	Cancer Deaths Averted per 1,000 women	False Positive Biopsies per 1,000 women
Biennial Screening 50 – 74 years	7.5	66
Annual Screening 50-74 years	12.2	132
Percent Increase	63%	100%

Mandelblatt et al. Ann Intern Med 2009; 151:738-747

# Effect of Screening Frequency on Stage of Disease

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- Less late stage disease with annual vs. biennial screening
  - Ages 65+ Field et.al., AJR, 1998
  - Ages 40-79 Hunt et.al., AJR, 1999
  - Ages 40-49 White et.al., JNCI, 2004
  - Ages 40-49 Ontilo et al, AJR, 2013
  - Ages 50 +
- No disease in late stage cancer with annual vs. biennial screening
  - Ages 50 + White et.al., JNCI, 2004

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## Potential Adverse Consequences of Screening

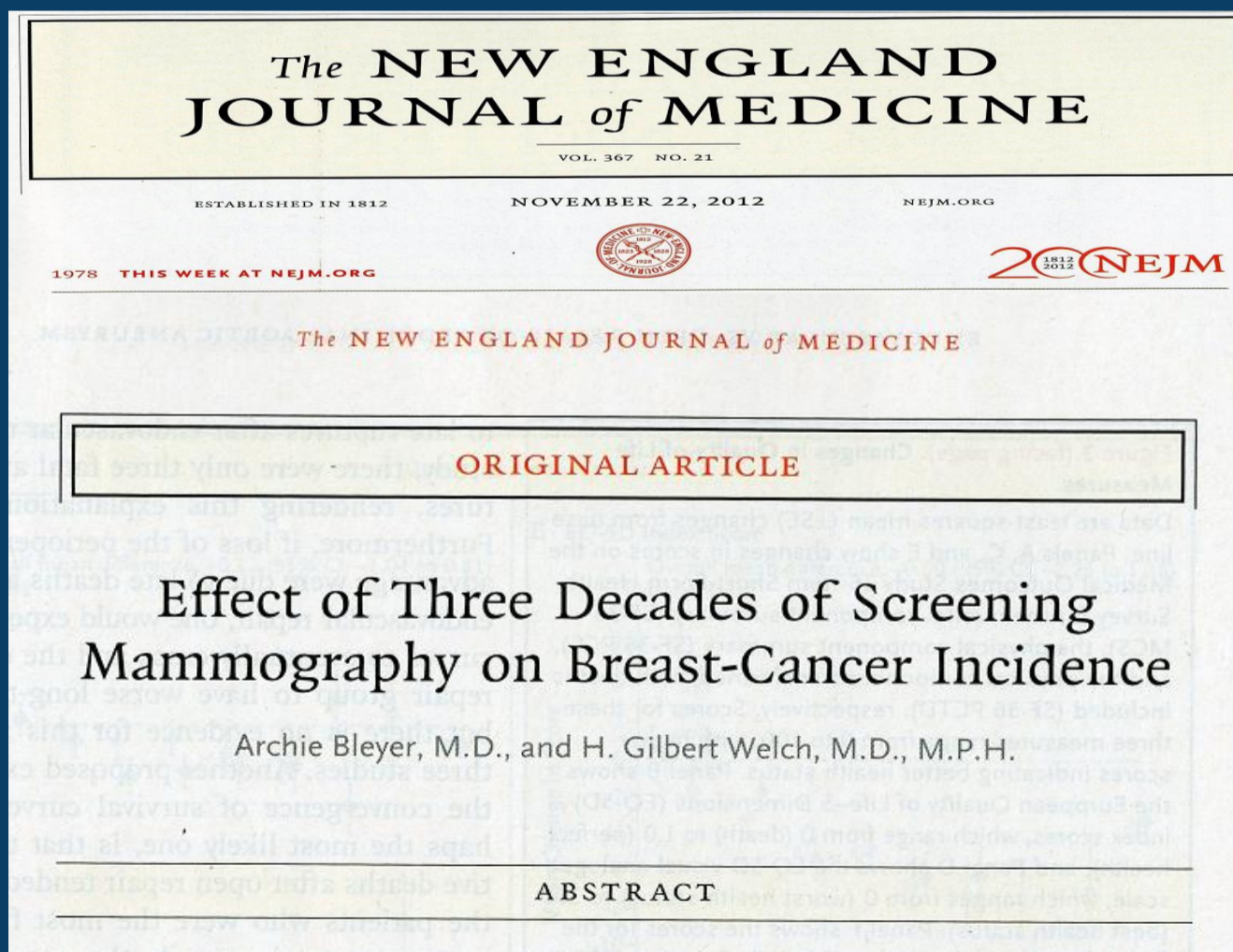
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- Overdiagnosis
- Excessive recall rates
- False positive biopsies
- DCIS?
- Radiation risk
- Psychologic effects
- Financial cost

# What is Meant by “Overdiagnosis”

- Some cancers detected at screening may not result in death because:
  - Slow growing
  - Non-lethal
  - Older patients may succumb to an unrelated co-morbid condition before they might die from breast cancer.
- Treatment of “overdiagnosed” tumors may cause unnecessary morbidity.

# What is Meant by “Overdiagnosis”



## How Did Bleyer and Welch Estimate an Overdiagnosis Rate of 31%?

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- Compared incidence of invasive cancer in pre-screening era vs screening era: 1976-1978 vs 2006-2008
- 128 per 100,000 in 2006-2008 was 31% higher than expected assuming a 0.25% increase from 1976-1978 in absence of screening

Bleyer and Welch. N Engl J Med 2012

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## Use of an Alternative Assumption Suggests No Evidence for Overdiagnosis

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- A 1% increase per year is consistent with 1940-1980 incidence data
- Using this, observed rate for 2006-2008 is actually lower than projected rate: 128 per 100,000 vs 132 per 100,000.

Garfinkel et al. Cancer 1994

Kopans. JACR 2013

# Overdiagnosis Estimates in Studies Having Adequate Adjustment for Lead Time and Risk

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	Invasive Only	Invasive and DCIS
• Denmark		4.8%
• Italy, North Central	3.2%	4.6%
• England, Wales	0.9%	
• Italy, Florence	0%	1.0%
• England	2.3%	
• Holland		2.8%

Olsen, Breast J 2006; Paci, Breast Cancer R, 2006; Waller, Cancer Epidemiol 2007; Puliti, Euro J. Cancer 2009; Duffy, Br J Cancer 2010; de Gelder, Epidemiol Rev 2011

# Overdiagnosis Estimates in Studies Having Adequate Adjustment for Lead Time and Risk

Original Article

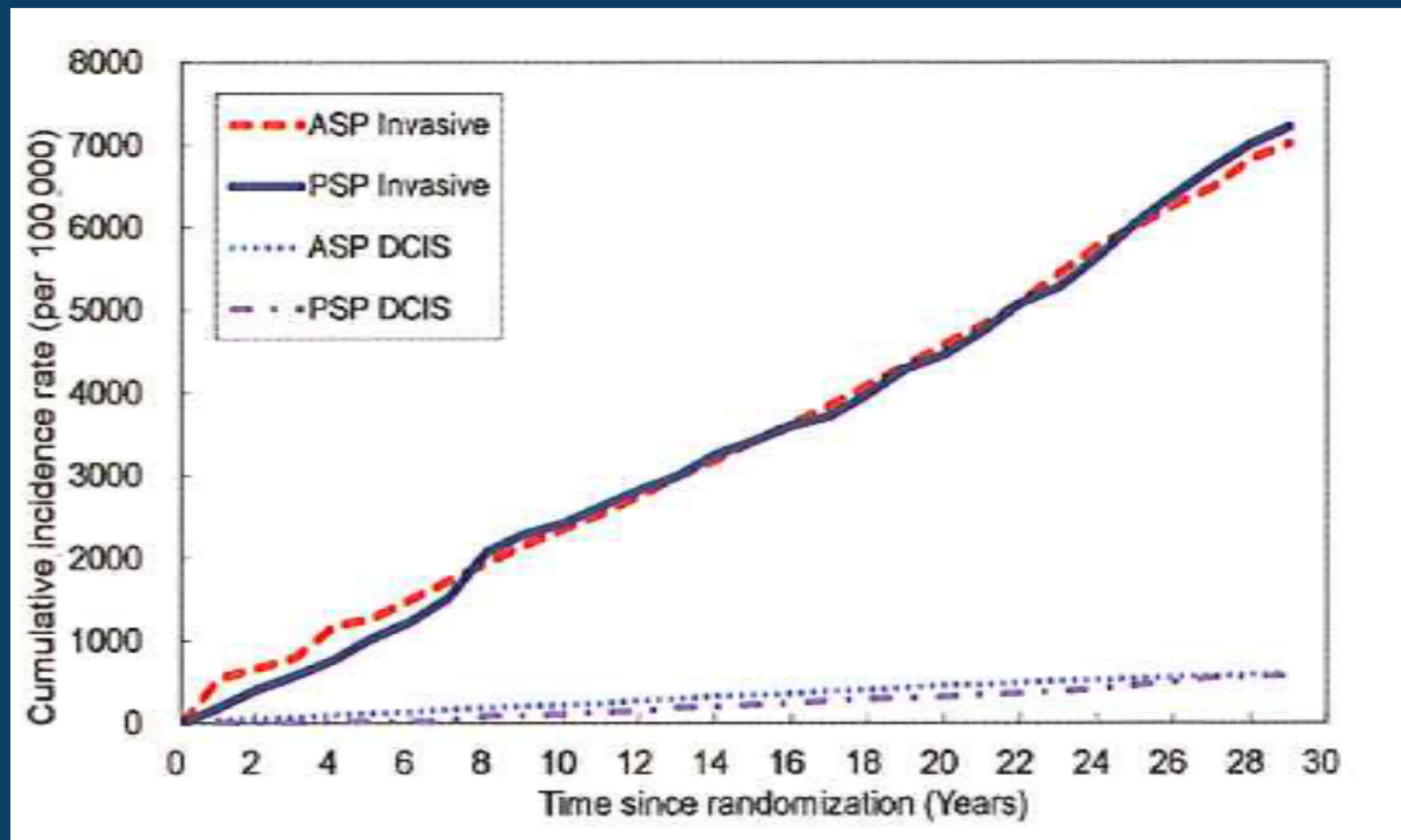
## Long-Term Incidence of Breast Cancer by Trial Arm in One County of the Swedish Two-County Trial of Mammographic Screening

Amy Ming-Fang Yen, PhD<sup>1</sup>; Stephen W. Duffy, MSc<sup>2</sup>; Tony Hsiu-Hsi Chen, PhD<sup>3</sup>; Li-Sheng Chen, PhD<sup>1</sup>; Sherry Yueh-Hsia Chiu, PhD<sup>4</sup>; Jean Ching-Yuan Fann, PhD<sup>5</sup>; Wendy Yi-Ying Wu, MS<sup>3</sup>; Chiu-Wen Su, BS<sup>3</sup>; Robert A. Smith, PhD<sup>6</sup>; and László Tabár, MD<sup>7</sup>

**BACKGROUND:** This study estimated the excess incidence (overdiagnosis) of breast cancer associated with starting mammographic screening at an earlier age, by using data from the Dalarna County component of the Swedish Two-County Trial of breast cancer screening. **METHODS:** In Dalarna County, Sweden, 38,589 women aged 40 to 74 years were randomized to invitation to regular mammographic screening (active study population [ASP]) and 18,582 women to usual care (passive study population [PSP]). After 3 screening rounds (6-8 years after randomization), the PSP was invited to screening. The cumulative incidence of breast cancer was calculated in the ASP and PSP from randomization to 29 years later. In addition, cumulative incidence was calculated for invasive cancers, advanced invasive cancers ( $\geq 2$  cm in maximum diameter or node-positive), and nonadvanced cancers ( $< 2$  cm and node negative). **RESULTS:** There was no excess of cancers in the ASP at 29 year follow-up (relative risk, 1.00; 95% confidence interval, 0.92-1.08). Cumulative incidence in the 2 arms approximately equalized at the conclusion of the first round of screening of the PSP. There was an excess of nonadvanced cancers and a deficit of advanced cancers in the ASP, both of which persisted to 29 years. **CONCLUSIONS:** There was no additional breast cancer incidence associated with 100,000 additional screens in the ASP. Results suggest that overdiagnosis is small and largely confined to the prevalence screen. *Cancer* 2012;118:5728-32. © 2012 American Cancer Society.

**KEYWORDS:** breast neoplasms, mammography, screening, randomized trials, overdiagnosis, Sweden.

# Cumulative 30 Year Incidence of Invasive and In Situ Cancers in Swedish Trial Study and Control Group



# Does Detection of Ductal Carcinoma in Situ Represent Overdiagnosis?

# How Often Will DCIS Progress to Invasive Disease?

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Screen	DCIS Type	
	Progressive	Non-progressive
Initial	63%	37%
Subsequent	96%	4%

Yen M-F, Tabar ., et al: Eur J Cancer 2003

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## CONCLUSIONS

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- The most reliable studies estimate that “overdiagnosis” is 0%-10%, not 30%
- However, even a 30% estimate does not annul the substantial mortality reduction found in screening trials because...
- Positive results from RCT’s are not negated by:
  - Length-biased sampling
  - Lead time bias
  - Selection bias
- Most DCIS is not overdiagnosis

# Cost Effectiveness of Medical Interventions

<b>Intervention</b>	<b>Mean Cost / Year of Life Gained</b>
<b>Antihypertensive Drugs</b>	<b>\$16,000</b>
<b>Annual Mammography, Age 40-60</b>	<b>\$17,000</b>
<b>Two-Vessel Coronary Bypass</b>	<b>\$28,000</b>
<b>Automobile Seatbelts and Airbags</b>	<b>\$32,000</b>
<b>Annual Pap-Smears from Age 21</b>	<b>\$50,000</b>
<b>Renal Dialysis</b>	<b>\$55,000</b>

Mammo data from Rosenquist and Lindfors. *Cancer* 1998;82: :2235-2340  
Other data from Tengs et al. *Risk Anal* 1995; 15:369-390

## **“Personalized Screening” Means Different Thing to Different People**

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- For most radiologists, it means annual mammography starting at age 40 plus supplementary screening with either MRI, breast ultrasound or tomosynthesis for those at high risk or with dense breasts.
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## **“Personalized Screening” Means Different Thing to Different People**

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- For some health care planners, “personalized screening” is a euphemism for screening some women less often, every 2, 3, or 4 years.
- These women are presumed to be at lower risk because of age, lower breast density, absence of family history, etc.

# What are the Shortcomings from Less Frequent Screening for Presumably Lower Risk Women?

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- Over 80% of breast cancers occur among women with no known risk factors
- Risk for women having heterogeneously dense breasts (BI-RADS 3), is only 1.5 x that for women with “scattered densities” (BI-RADS 2)
- Radiologists cannot reliably differentiate density 2 vs 3 at mammography.

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## Psychologic Effects of Screening Mammography

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- 99% of women believe that false positive mammography is an acceptable risk to save lives
- 63% of women believe that 500 or more false-positive results are acceptable for each life saved

Schwartz et al, JAMA 2004; 291:71-78.

# Radiation Risk from Screening Mammography?

## **Excess Breast Cancers Among Women Exposed to High Doses**

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- Atomic bomb survivors
  - Postpartum mastitis
  - Pulmonary tuberculosis
  - Hodgkin's disease
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## **Excess Breast Cancers Among Women Exposed to High Doses**

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No woman has ever been shown to have developed breast cancer as a result of mammography, even from multiple studies received over many years and at doses much higher than those from current technique.

# How Does the Hypothetical Radiation Risk from Mammography Compare with the Known Proven Benefit from Screening?

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“At current mammography radiation dose, even a 1% reduction in mortality confers more benefit than risk... and a mortality reduction of 20% to 40% lends to a substantial decrease in the number of deaths or years lost.”

National Council on Radiation Protection and Measurements. “A Guide to Mammography and Other Breast Imaging Procedures.” NCRP Report No. 149, NCRP 2004.

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## One Final Observation...

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The current confusion, misunderstanding, and controversy could have been prevented by simply reading and understanding the screening mammography literature, and placing the health and well being of our patients first.