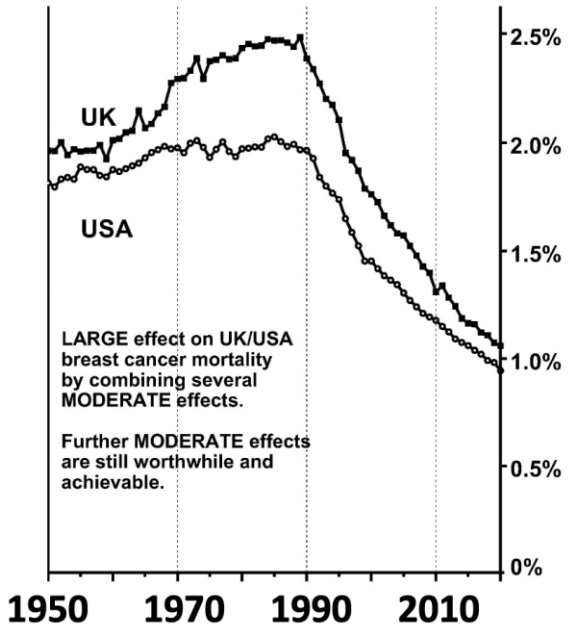
Lessons From Breast Cancer Research and Remaining Gaps

Reshma Jagsi, MD, DPhil
Chair, Department of Radiation Oncology
Emory University School of Medicine

Striking Mortality Improvements Reflect the Accumulation of Multiple Moderate Gains from Improvements in Screening and Treatment

UK/USA breast cancer mortality trends, 1950-2020



Probability* that a 35-year-old woman will die before 70 from breast cancer

*if no other causes existed, and the age-specific breast cancer death rates in the calendar year of interest stayed constant

Slide from Sir Richard Peto, University of Oxford, Early Breast Cancer Trialists Collaborative Group, used with permission

Focusing on Treatment Optimization

- Perhaps more than for any other type of cancer, the management of breast cancer has been supported by a steady trajectory of research that has discovered ways to:
  - safely de-escalate therapy and
  - identify patients who may safely forego potentially toxic treatments
- Government funding of research is especially important when less may be more
  - fewer sources of industry support for such efforts (unless patient selection is being driven by a proprietary test or technology)

Asia's Ascent — Global Trends in Biomedical R&D Expenditures

Justin Chakma, B.Sc., Gordon H. Sun, M.D., Jeffrey D. Steinberg, Ph.D., Stephen M. Sammut, M.A., M.B.A., and Reshma Jagsi, M.D., D.Phil.

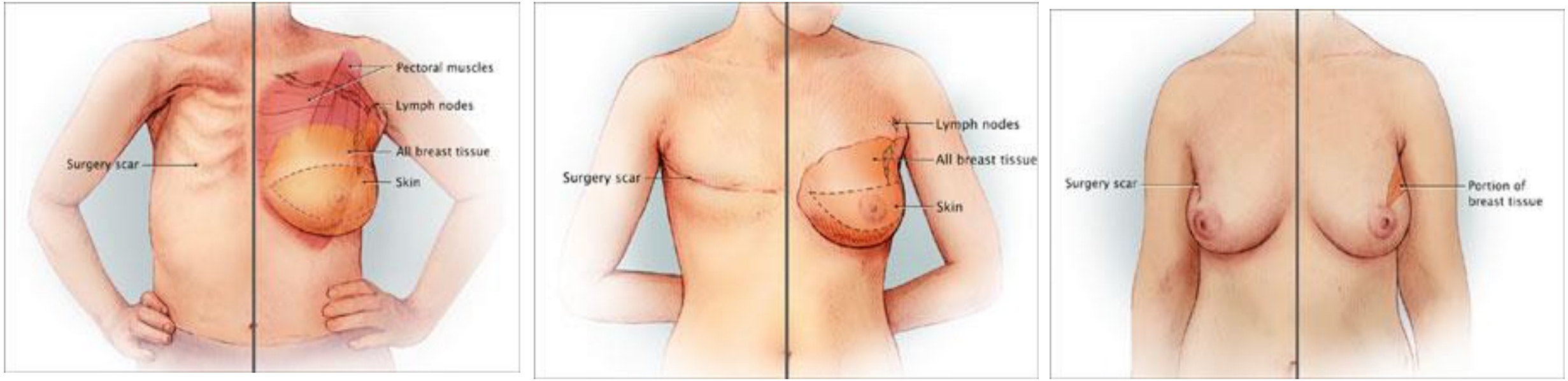
The NEW ENGLAND JOURNAL of MEDICINE

The Calculus of National Medical Research Policy — The United States versus Asia

Gordon H. Sun, M.D., Jeffrey D. Steinberg, Ph.D., and Reshma Jagsi, M.D., D.Phil.

NIH-Funded Discoveries: Optimizing Surgery

- From Radical Mastectomy to MRM to BCT

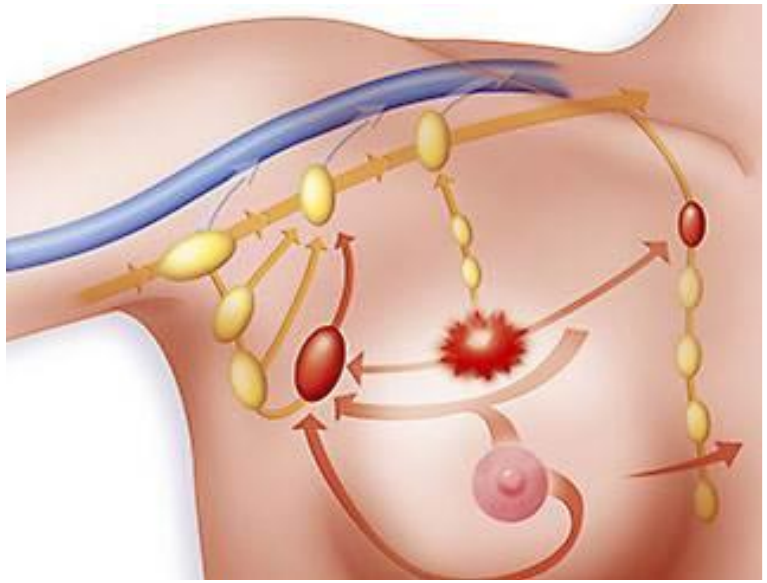


RCTs of MRM vs BCT: Milan 1973; NSABP B-06 1976; EORTC 1980; DBCG 82TM 1983; NCI 1979; IGR 1972

NIH-Funded Discoveries: Optimizing Surgery

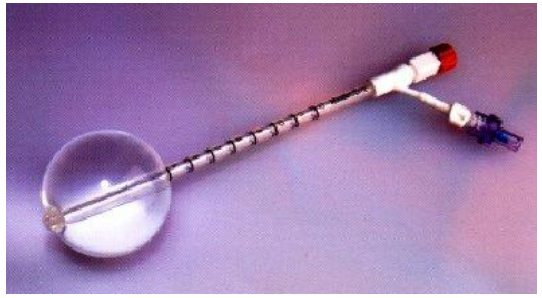
- From ALND to SLNB:

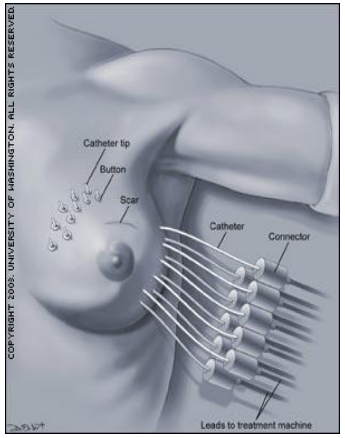
- INRC Genova (1998)
- IEO Milan (1998)
- NSABP B-32 (1999)
- GISCRIS (1999)
- Almanac Cardiff (1999)
- GIVOM (1999)
- Cambridge/East Anglia (1999)
- ACOSOG Z0011 (1999)
- IBSCG 23-01 (2001)
- AATRM (2002)
- KiSS (2000)
- RACs Auz-NZ SNAC (2001)
- PIOFG (2001)
- HC Lyon GF-GS01 (2003)
- Padova (2003)
- RACs Auz-NZ SNAC2 (2006)



NIH-Funded Discoveries: Optimizing RT

- From longer to shorter courses:
  - Hypofractionated whole breast irradiation
    - Large RCTs (e.g., START A & B, Canadian trials)
  - Accelerated partial breast irradiation
    - Multiple large RCTs including NSABP B39/RTOG 0413





NIH-Funded Discoveries: Optimizing RT

- Omission of RT altogether
  - Among older women with ER+ early-stage disease (CALGB 9343, PRIME II)
  - Newer trials focused on tumor biology
    - IDEA (US)
    - PRECISION (US)
    - LUMINA (Canada)
    - EXPERT (ANZ)
    - PRIMETIME (UK)
    - NRG BR007 (US)

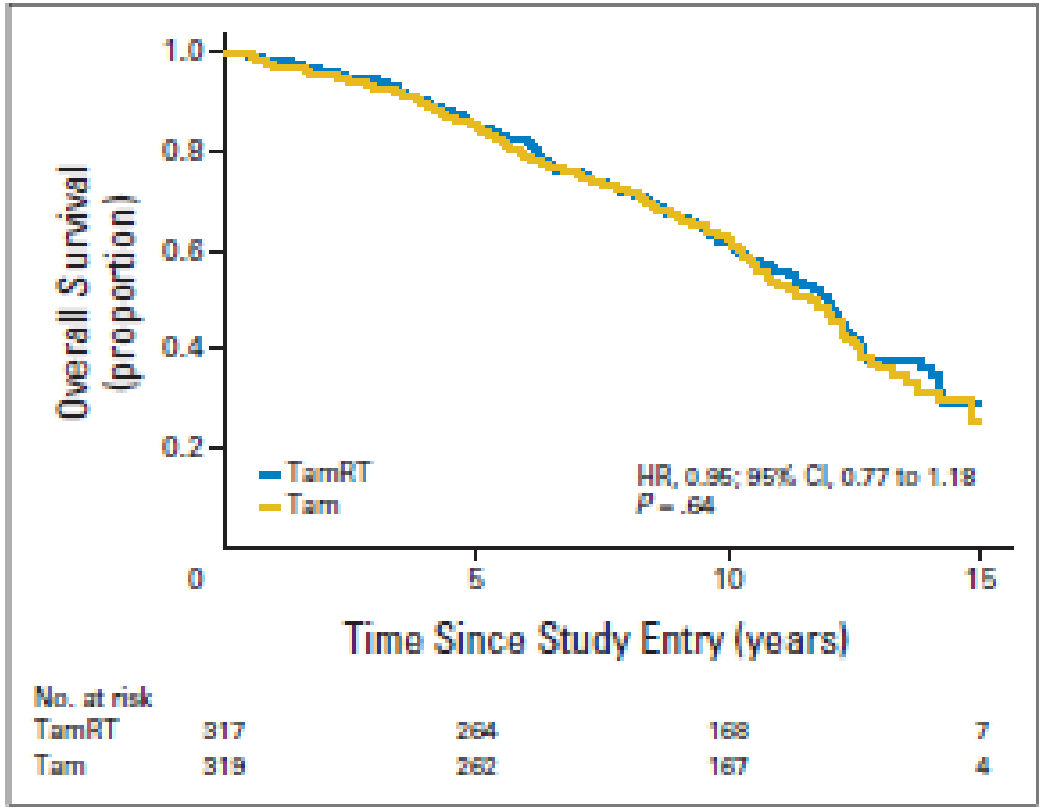
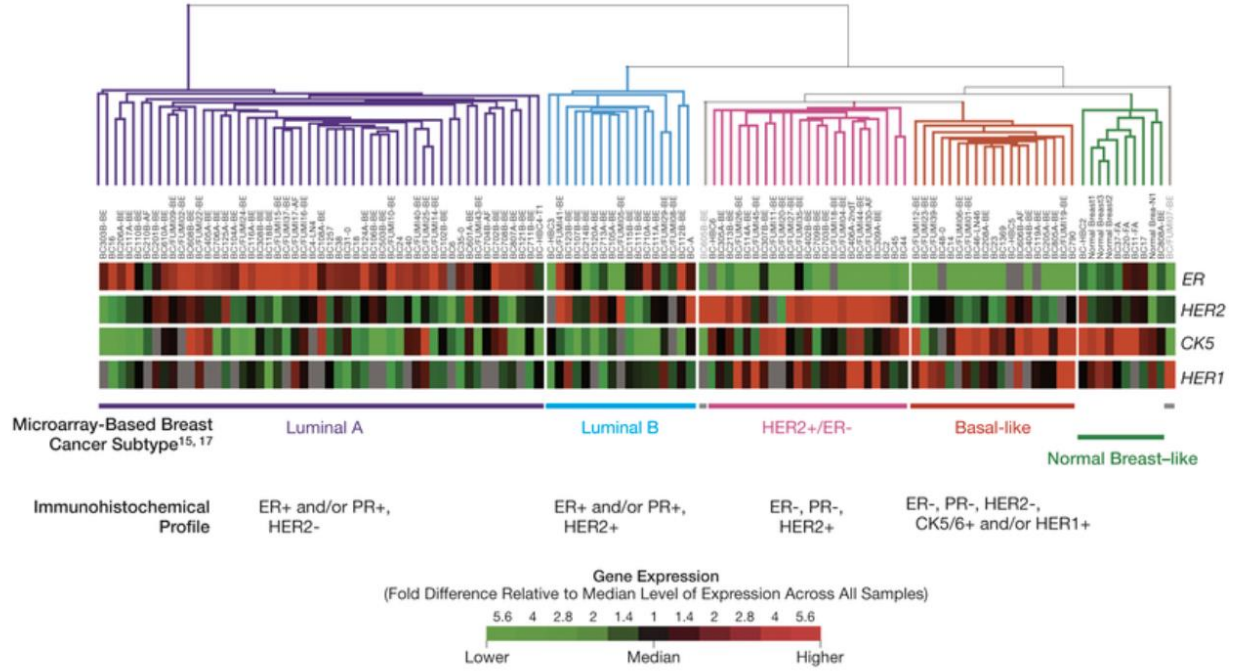


Fig 5. Overall survival. HR, hazard ratio; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

NIH-Funded Discoveries: Growing Appreciation of Biological Heterogeneity

Figure 1. Immunohistochemical Identification of Breast Tumor Intrinsic Subtypes



- *Carey, Perou, et al. JAMA 2006*
- This work was supported by an award to the University of North Carolina for a Breast Cancer Specialized Program of Research Excellence (SPORE) from the National Cancer Institute (NIH/NCI P50-CA58223), a grant from the General Clinical Research Centers Program of the Division of Research Resources/National Institutes of Health (M01RR00046 awarded to Dr Carey), and by the NCI (R01-CA-101227-01 awarded to Dr Perou).

NIH-Funded Discoveries: Optimizing Systemic Therapy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 12, 2018 VOL. 379 NO. 2

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

21-Gene Assay to Inform Chemotherapy Benefit in Node-Positive Breast Cancer

Kevin Kalinsky, M.D., William E. Barlow, Ph.D., Julie R. Gralow, M.D., Funda Meric-Bernstam, M.D., Kathy S. Albain, M.D., Daniel F. Hayes, M.D., Nancy U. Lin, M.D., Edith A. Perez, M.D., Lori J. Goldstein, M.D., Stephen K.L. Chia, M.D., Sukhbinder Dhesy-Thind, M.D., Priya Rastogi, M.D., et al.

Our Work is Not Done

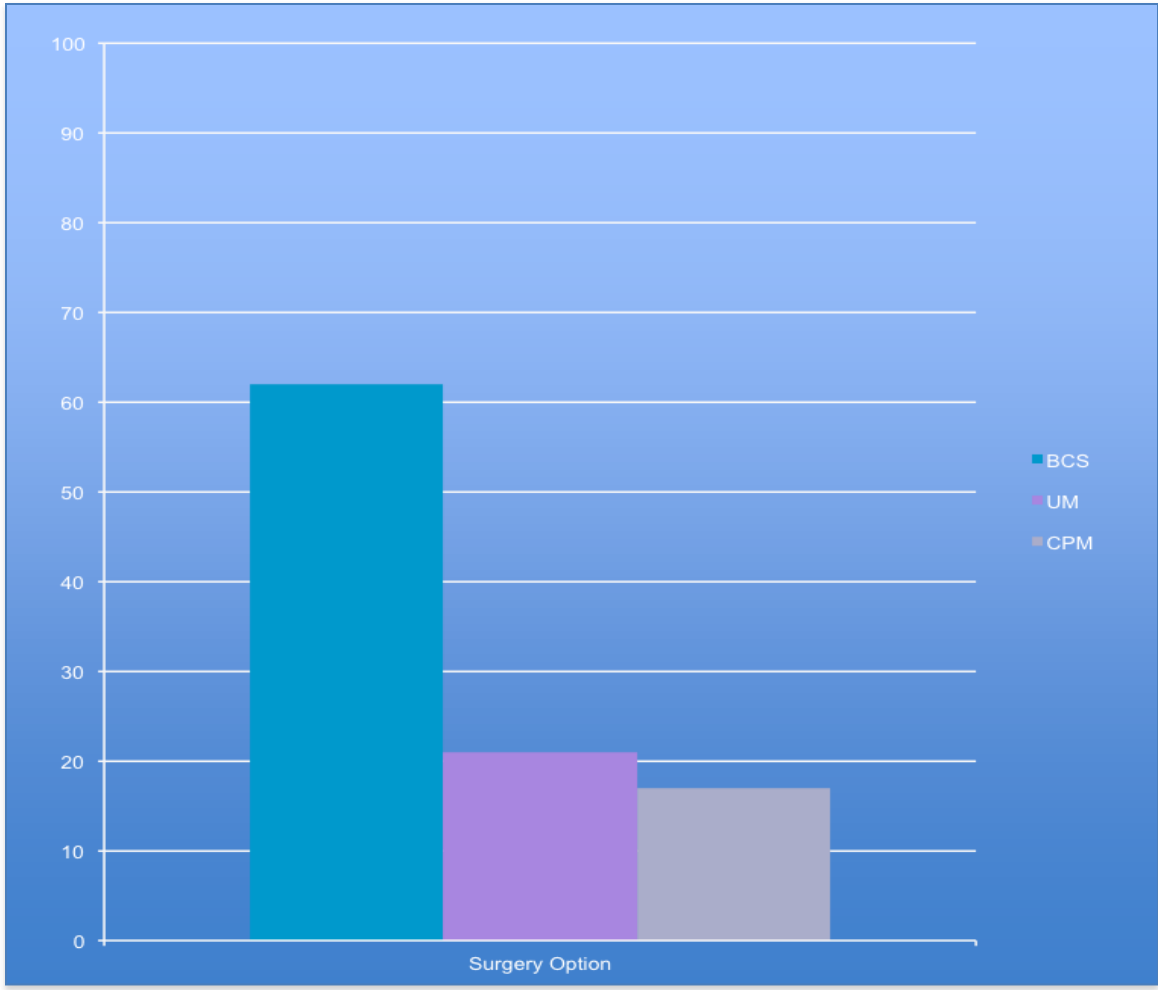
- Key gaps remain in translating discoveries into practice
- Despite robust evidence showing that many women can safely be spared potentially toxic treatments…
  - Many women diagnosed with breast cancer today pursue considerably more aggressive treatments than needed to achieve excellent outcomes in terms of survival and recurrence

Contralateral Prophylactic Mastectomy

Jagsi et al. JAMA Surgery 2017.

The JAMA Network

- Among pts with early-stage breast cancer identified by LA & Georgia SEER in 2013-14: 62% received BCS, 21% unilateral mastectomy, and 17% bilateral mastectomy with CPM
- Even among women without a deleterious genetic mutation or FH in multiple relatives, 14% received CPM



CanSORT

www.cansort.org

iCan care

Slow Adoption of RT Hypofractionation

Adoption of Hypofractionated Radiation Therapy for Breast Cancer After Publication of Randomized Trials

Reshma Jagsi, MD, DPhil,* Aaron D. Falchook, MD,† Laura H. Hendrix, MS,† Heather Curry, MD,‡ and Ronald C. Chen, MD, MPH†

*Department of Radiation Oncology, University of Michigan Medical School, Ann Arbor, Michigan; †Department of Radiation Oncology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and ‡Radiation Oncology, Eviti, Inc, Philadelphia, Pennsylvania

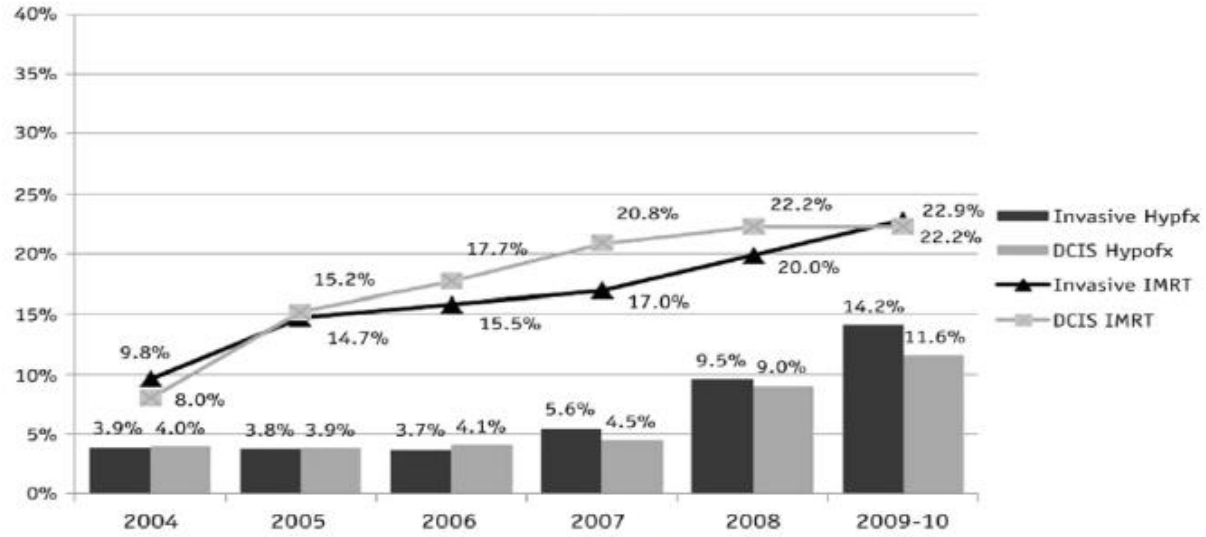


Fig. 1. Rates of hypofractionated radiation therapy and IMRT use over time. DCIS = ductal carcinoma in situ; IMRT = intensity modulated radiation therapy.

The Perils of Overtreatment: Worsened QoL

VOLUME 36 · NUMBER 25 · SEPTEMBER 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

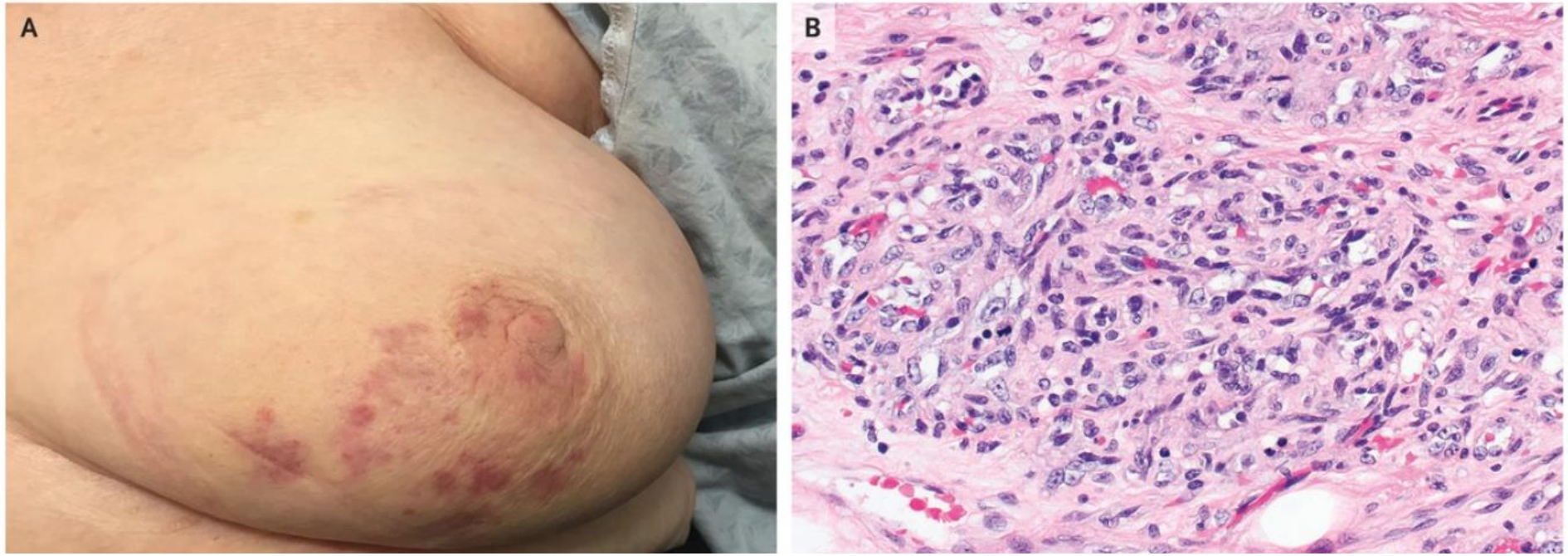
Prospective Study of Psychosocial Outcomes of Having Contralateral Prophylactic Mastectomy Among Women With Nonhereditary Breast Cancer

Patricia A. Parker, Susan K. Peterson, Yu Shen, Isabelle Bedrosian, Dalliah M. Black, Alastair M. Thompson, Jonathan C. Nelson, Sarah M. DeSnyder, Robert L. Cook, Kelly K. Hunt, Robert J. Volk, Scott B. Cantor, Wenli Dong, and Abenaa M. Brewster

The Perils of Overtreatment: Lymphedema

Photo courtesy David Byrd

The Perils of Overtreatment: Second Malignancy



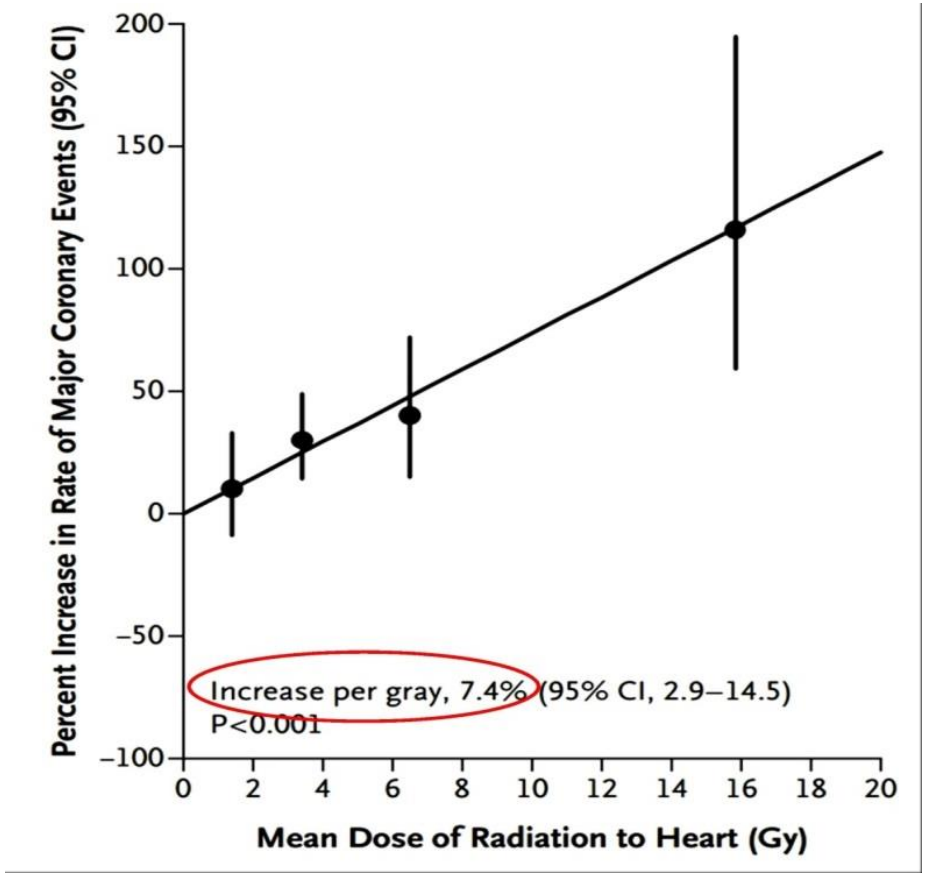
IMAGES IN CLINICAL MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

Radiation-Induced Angiosarcoma after Breast-Cancer Treatment

Jennifer K. Plichta, M.D., and Kevin Hughes, M.D.

The Perils of Overtreatment: Cardiac Toxicity



Darby S et al., NEJM 2013.

3-yr Adjusted Incidence Rate Ratios for Heart Failure or Cardiomyopathy: SEER-Medicare

Chemotherapy/biologic therapy			
Trastuzumab	**1.78**	**1.43–2.21**	**<0.001**
Anthracycline + trastuzumab	**2.32**	**1.87–2.87**	**<0.001**
Anthracycline	**1.12**	**1.02–1.23**	**0.021**

Chen J et al., JACC 2012.

The Perils of Overtreatment: Fatigue, Neurotoxicity, & Cognitive Decline

Fatigue in Breast Cancer Survivors: Occurrence, Correlates, and Impact on Quality of Life

By Julienne E. Bower, Patricia A. Ganz, Katherine A. Desmond, Julia H. Rowland, Beth E. Meyerowitz, and Thomas R. Belin

Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline Summary

Dawn L. Hershman, MD, MS, Christina Lacchetti, MHSc, and Charles L. Loprinzi, MD

Cancer-Related Cognitive Outcomes Among Older Breast Cancer Survivors in the Thinking and Living With Cancer Study

Jeanne S. Mandelblatt, Brent J. Small, Gheorghe Luta, Arti Hurria, Heather Jim, Brenna C. McDonald, Deena Graham, Xingtao Zhou, Jonathan Clapp, Wanting Zhai, Elizabeth Breen, Judith E. Carroll, Neelima Denduluri, Asma Dilawari, Martine Extermann, Claudine Isaacs, Paul B. Jacobsen, Lindsay C. Kobayashi, Kelly Holohan Nudelman, James Root, Robert A. Stern, Danielle Tometich, Raymond Turner, John W. VanMeter, Andrew J. Saykin, and Tim Ahles

The Perils of Overtreatment: Financial Toxicity

Long-Term Financial Burden of Breast Cancer: Experiences of a Diverse Cohort of Survivors Identified Through Population-Based Registries

Reshma Jagsi, John A.E. Pottow, Kent A. Griffith, Cathy Bradley, Ann S. Hamilton, John Graff, Steven J. Katz, and Sarah T. Hawley

JOURNAL OF CLINICAL ONCOLOGY

HealthAffairs

At the Intersection of Health, Health Care and Policy

By Scott Ramsey, David Blough, Anne Kirchhoff, Karma Kreizenbeck, Catherine Fedorenko, Kyle Snell, Polly Newcomb, William Hollingworth, and Karen Overstreet

Washington State Cancer Patients Found To Be At Greater Risk For Bankruptcy Than People Without A Cancer Diagnosis

Where We Must Go: Decision Support

VOLUME 36 · NUMBER 7 · MARCH 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

Improving Breast Cancer Surgical Treatment Decision Making: The iCanDecide Randomized Clinical Trial

Sarah T. Hawley, Yun Li, Lawrence C. An, Kenneth Resnicow, Nancy K. Janz, Michael S. Sabel, Kevin C. Ward, Angela Fagerlin, Monica Morrow, Reshma Jagsi, Timothy P. Hofer, and Steven J. Katz

Where We Must Go: Decision Support

FIGURE 2. CONCEPTUAL FRAMEWORKS: SUMMARY OF HOW SharES WILL IMPACT PRIMARY AND SECONDARY OUTCOMES

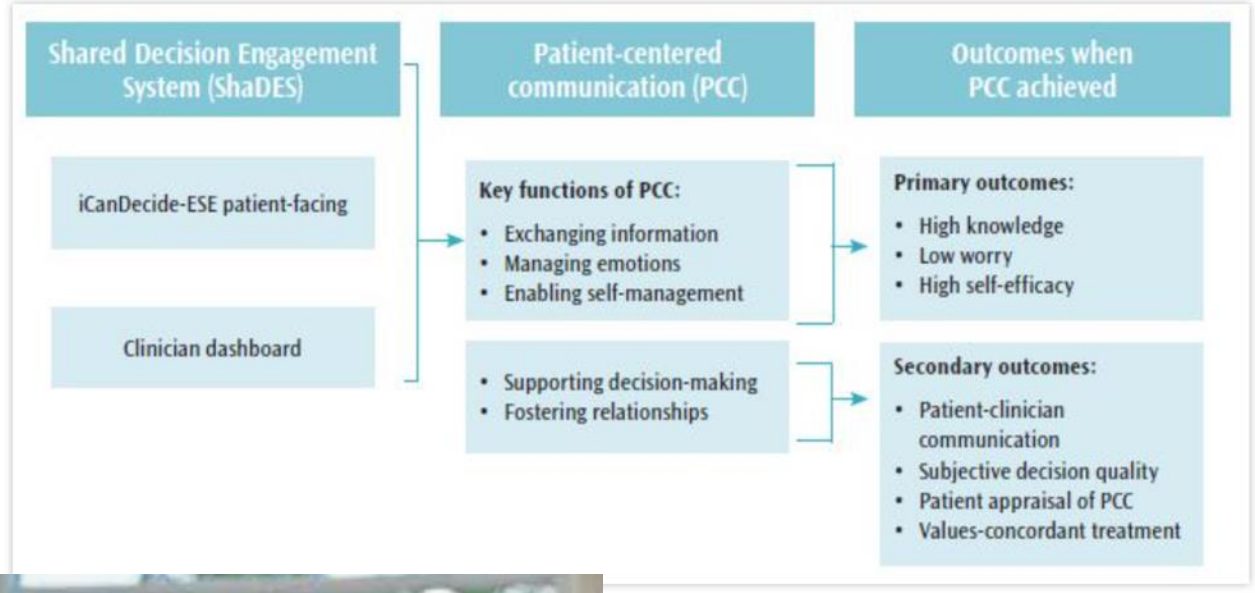
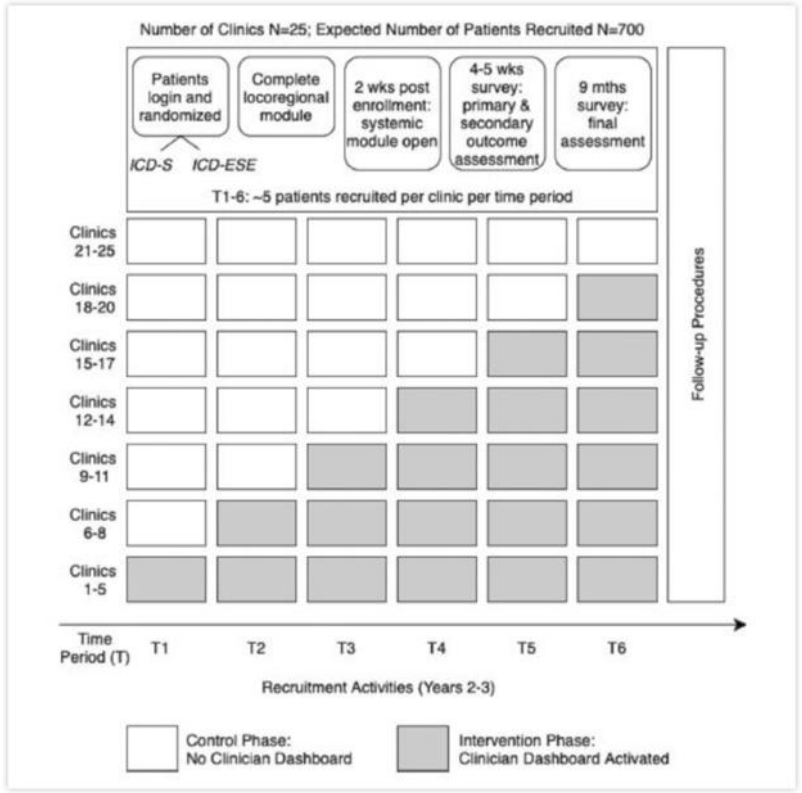


FIGURE 3. STEPPED-WEDGE CLUSTER TRIAL DESIGN OF SharES (A231901CD)



- Improving Patient-Centered Communication in Breast Cancer: A Randomized Control Trial of a Shared Decision Engagement System (SharES) (Alliance 231901CD).
- Funded by NCI R01 CA237046, PIs Hawley & Jagsi
- Activated January 15, 2021, at 25 National Community Oncology Research Program sites. Accrual goal 700 patients.

Equity in Care Delivery is Essential

- In addition to general efforts to address overtreatment and empower patients in decision-making, striking disparities require attention
- Advances like AI require especially thoughtful investigation from this perspective
- The Lancet's Breast Cancer Commission report is forthcoming in April
  - Subtitled: "Tackling a Global Health, Gender, and Equity Challenge"
  - No spoilers, but the work needed to address breast cancer is far from done, and that's not just in other parts of the world—it's true here in the US too

Where We Must Go: Target Racial/Ethnic Disparities

- Although the breast cancer death rate for all women has gone down by 40% since 1988, but not all groups have benefited the same from advances in screening and treatment
- Currently, the breast cancer death rate is 40% higher in Black women versus White women in the US
- Aggregate reporting of API limits ability to detect meaningful differences there

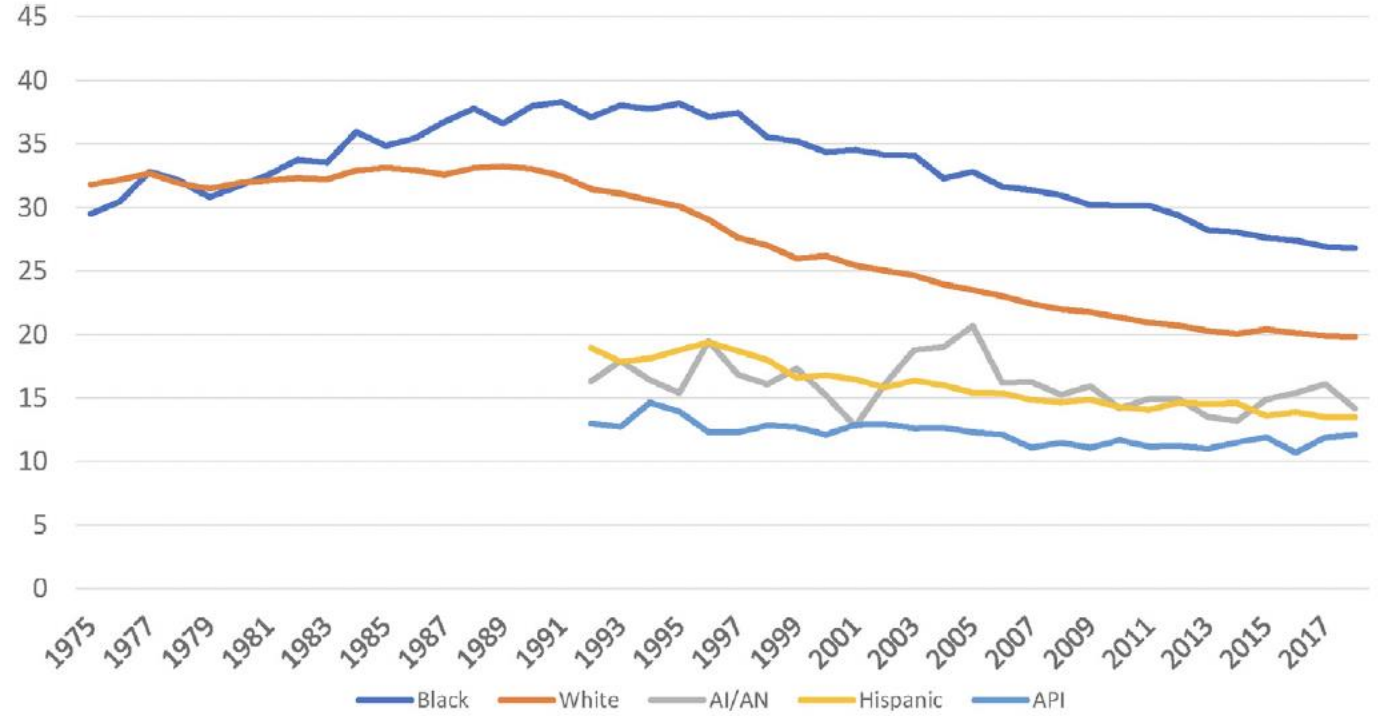


Fig. 2. Breast cancer death rate by race/ethnicity, 1975 to 2017.

Grabinski & Brawley, Disparities in Breast Cancer, Obstet Gynecol Clin N Am 49 (2022) 149–165.

Where We Must Go: Focus on Older Adults

- Among the estimated 268,600 American women diagnosed annually with breast cancer, 83,200 are older than 70 years, and this number is growing
- Thanks to recent research, two age-specific local treatment recommendations for ER+ BC in women older than 70 years have emerged
  - i) to consider omission of RT after lumpectomy
  - ii) to omit axillary surgery in patients intending to receive ET
- No similar age-specific recommendation to tailor the use of endocrine therapy has emerged
  - The standard systemic therapy for older postmenopausal women with Stage 1 ER+ BC in is ET (tamoxifen or aromatase inhibitor) for 5 years

Where We Must Go: Metastatic Disease

- Need better data: SEER should collect information on recurrences
- Focus on early-stage disease (like all of my slides) alienates many patients with MBC, who feel that they have “failed” at cure and feel feel isolated and abandoned
  - Language like “survivorship” (and “failure”) can be isolating and hurtful
- Some patients with MBC may even be curable, and for others, access to treatment may prolong longevity and improve quality of life
- MBC patients can now live many years: their needs must not be forgotten!

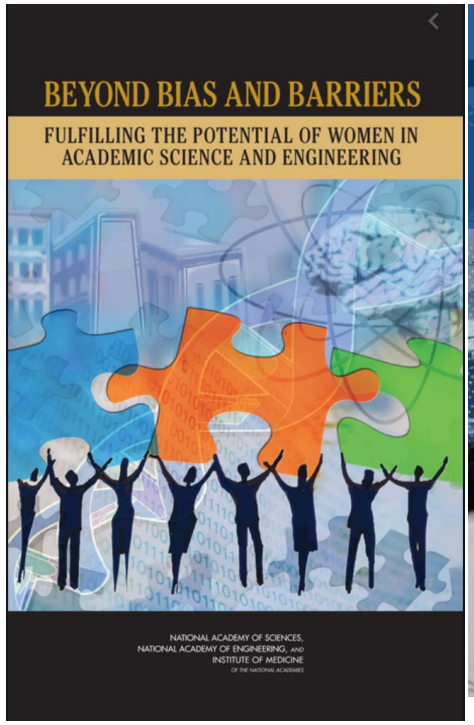
Where We Must Go: Prevention

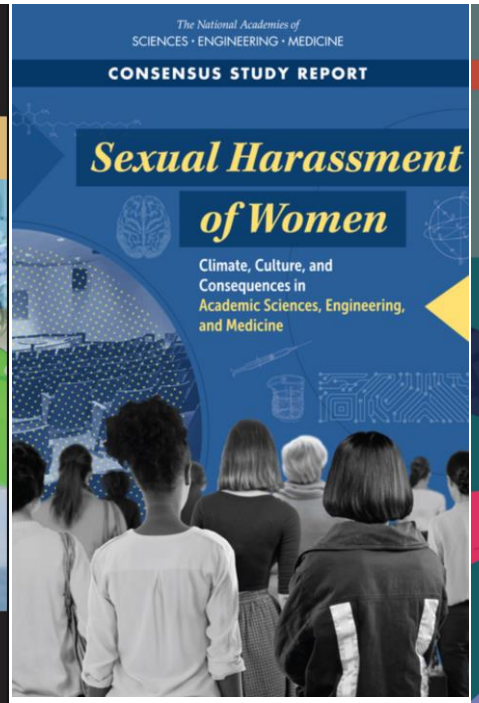
- Efforts must consider ways to target known exposures that elevate risk, including alcohol, and to support behaviors that reduce risk, including lactation and physical activity
- The NCI's evidence-based cancer control programs are a promising step in the right direction

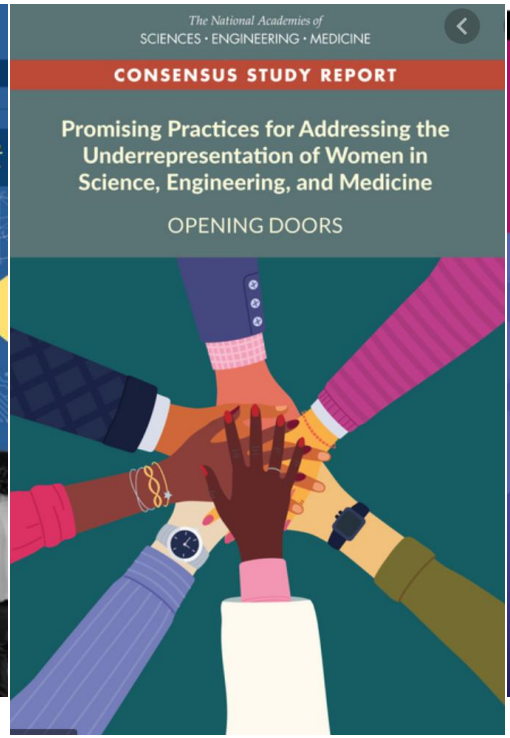
A Thriving Workforce to Pursue Women's Health is Key

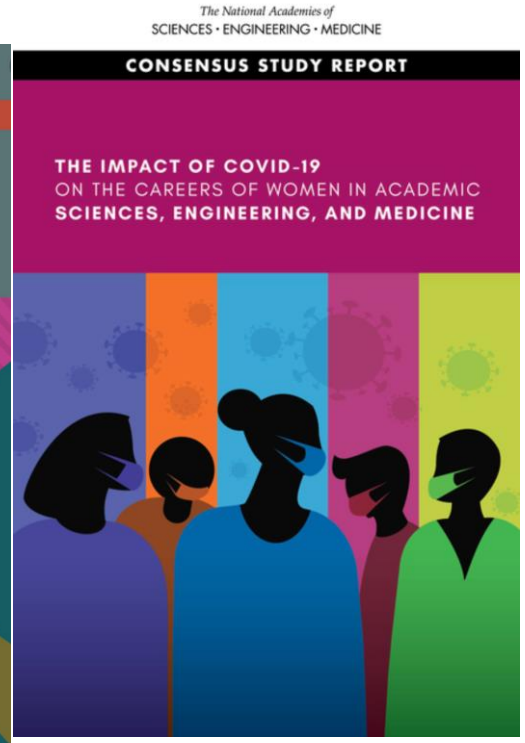
- Research on women's health is often pursued by women investigators
- Essential to support ORWH's ongoing efforts to understand gender differences in experiences and career trajectories of biomedical research workforce
- With R01 grants developed by ORWH, my team has shown that women clinician-investigators with K08 and K23 awards are
  - Less likely to attain R01 grants (Ann Intern Med 2009)
  - Paid less & receive fewer resources (JAMA 2012, Acad Med 2013, JGIM 2015)
  - Less likely to receive sponsorship (JAMA Internal Med 2017)
  - More likely to experience sexual harassment (JAMA 2016, JAMA 2023)
  - Spend 8h more per week on parenting and domestic tasks (Ann Intern Med 2014)
  - More likely to experience burnout (JAMA Internal Med 2020)

Key NASEM CWSEM Contributions









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The Impact of Burnout on Gender Equity in Science, Engineering, and Medicine: A Workshop Series

Conclusions

- Breast cancer mortality has decreased thanks to advances in screening and treatment (not one big leap but rather accumulation of multiple moderate gains)
- Numerous strategies to individualize treatment have been evaluated in trials, further increasing the ability to cure while preserving quality of life
- Federal funding of research regarding breast cancer remains essential, especially in the increasingly common cases where less may be more and overtreatment continues in practice
- Interventions must be developed and evaluated to support patients as they navigate emotionally charged decisions and overwhelming abundance of complex risk information generated by all of the great research
- Unacceptable disparities remain, both by race and for older adults, that require targeted intervention
- Metastatic disease must not be ignored
- Prevention merits attention
- A vibrant workforce to continue addressing remaining gaps remains essential