# Women's Health 2024 | Beyond the Annual Visit

# *Breast Cancer Screening and Prevention for Average-Risk Patients*

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Global Learning Collaborative || Omnia Education
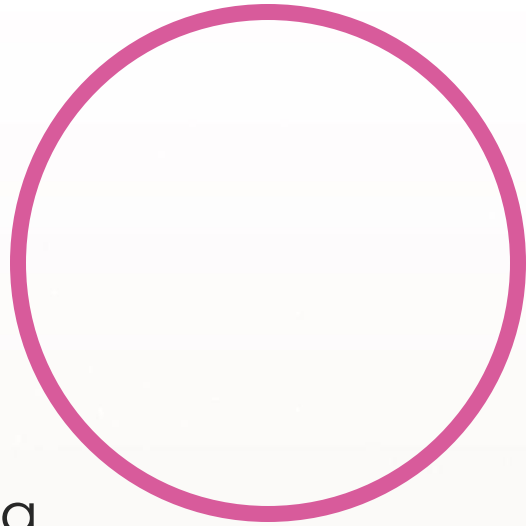
# Conflict of Interest Disclosure
# Anita L. Nelson, MD

| | |
|---|---|
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# Learning Objectives

**At the conclusion of this presentation,
the participant will be able to:**

- Identify factors that increase a woman's risk for developing breast cancer

- List methods for screening women for early breast cancer and explain the implications of early or more frequent breast cancer screening tests

- Create counseling strategies on preventive measures available to reduce the risk of breast cancer among those whose estimates for breast cancer are above normal (moderate-risk patients)

# GYN Carcinoma Incidence in US Women, 2024

| Carcinoma | New Cases | Deaths |
| --- | --- | --- |
| Ovarian | 19,680 | 12,270 |
| Uterine corpus | 67,880 | 13,250 |
| Uterine cervix | 13,820 | 4,360 |
| Vulvar | 6,900 | 1,630 |
| Vaginal & other | 8,650 | 1,870 |
| Breast | 310,720 | 42,250 |

https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/2024-cancer-facts-figures.html
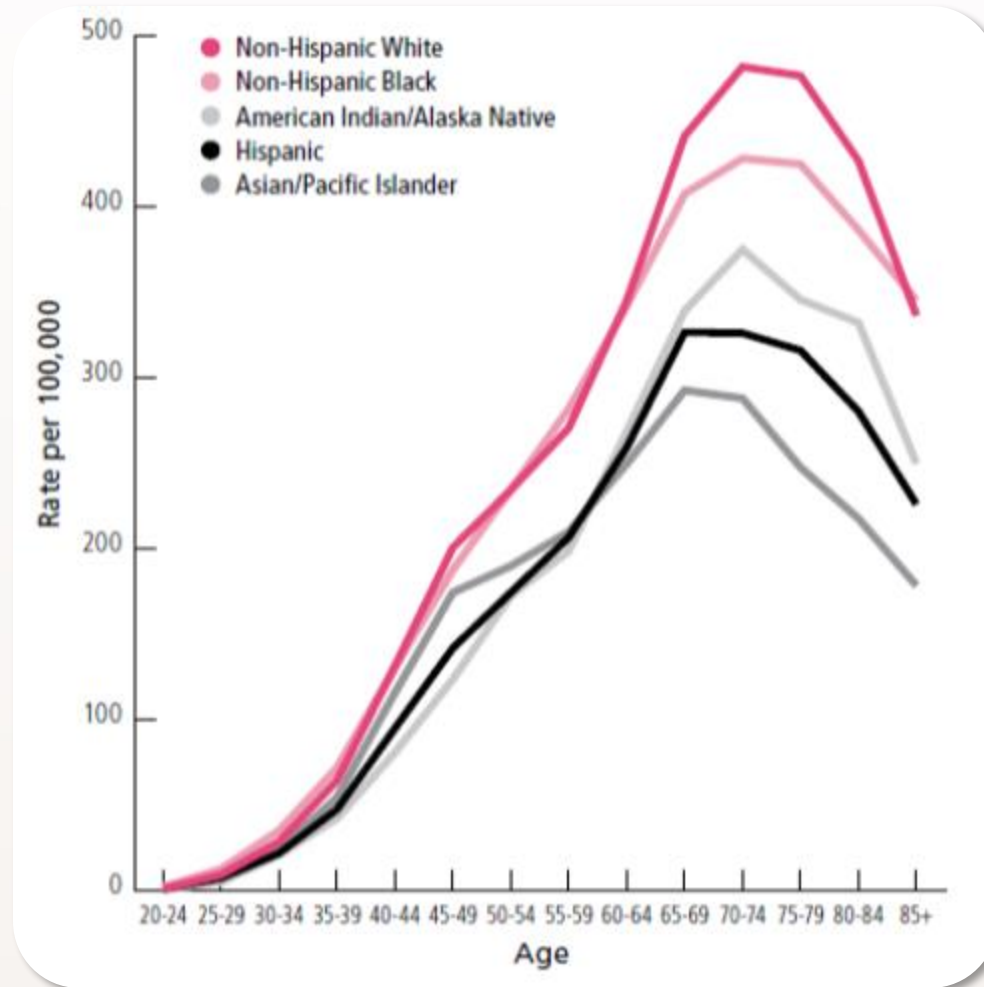
# *Breast Cancer Mortality Rate Trends*

- Meaningful progress has been made in reducing breast cancer deaths in the last 50 years
    - 58% decrease in mortality rate (deaths/100,000)
- What is responsible for reduction?
    - 29% from treatment of metastatic disease
    - 47% from treatment of stage I-III disease
    - 25% from mammographic screening
- Treatments: less aggressive surgeries, more targeted medications
- Invasive breast cancer is the second leading cause of cancer death and results in more years of life lost than any other cancer

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# *Disparities*

- Black women vs White women[1]
  - More likely to be diagnosed at a younger age and beyond stage I
  - 40% more likely to die from breast cancer
    - Delays in diagnosis and treatment contribute to mortality more than screening differentials
    - Higher incidence of negative hormone markers
    - Disparities in follow-up and treatment

- Sex and gender minority groups[2]
  - Greater delay to diagnosis
  - Higher rates of recurrence

1. USPSTF, Nicholson WK, et al. *JAMA*. 2024;331(22):1918-1930.
2. Eckhert E, et al. *JAMA Oncol*. 2023;9(4):473-480.

# Age-Specific Female Breast Cancer Incidence Rates by Race/Ethnicity, US, 2012-2016

# *Breast Cancer Incidence Changes*

- 5-year adjusted incidence rate per 100,000 women
  - Non-Hispanic White – 137.6
  - Black – 129.6

- Incidence in 40- to 49-year-olds is increasing – impacts screening recommendations
  - 2010-2019: incidence increased 2% per year
    - Similar self-reported rates of screening
      - 78% vs 84.5%

USPSTF, Nicholson WK, et al. *JAMA*. 2024;331(22):1918-1930.

# *Basic Features: Breast Cancer*

- Dividing time for the most common breast cancer (ductal carcinoma) is 100 days

- Time it takes from emergence of first cancer cell until diameter of mass is
  - 1 mm: when it might be seen on mammography – 8 years
  - 1 cm: when it could be palpated by clinician – 10 years
  - 2.5 cm: when patient is most likely to first detect – 12 years

- Consequences – many small cancers cannot be detected but provides basis for prevention
  - Not able to rule out clinically insignificant cancer with any imaging test

# Risk Factors for Breast Cancer

- For premenopausal and postmenopausal women
  - **Age**
  - **Breast density**
  - Family history of breast cancer
  - Prior breast procedure or chest irradiation
- Additional factors only for postmenopausal women
  - Race, ethnicity
  - BMI
  - Natural menopause
  - Hormone therapy > 5 years
  - Prior false positive mammogram
  - Weight gain > 5%

Barlow WE, et al. *J Natl Cancer Inst.* 2006;98(17):1204-1214.
Neuhouser ML, et al. *JAMA Oncol.* 2015;1(5):611-621.

# Breast Cancer Risk Factors in Women

| Relative Risk | Factor |
|---|---|
| **>4.0** | Age 65+ vs <65 years, although risk increases across ages until age 90 |
| | Biopsy-confirmed atypical hyperplasia |
| | Certain inherited genetic mutations for breast cancer (BRCA1 and/or BRCA2) |
| | Mammographically dense breasts |
| | Personal history of breast cancer |
| **2.1-4.0** | High endogenous estrogen or testosterone levels |
| | High bone density (postmenopausal) |
| | High-dose radiation to chest |
| | Two first-degree relatives with breast cancer |

American Cancer Society. Surveillance Research; 2011.

# Breast Cancer Risk Factors in Women

| Relative Risk | Factor |
|---|---|
| 1.1-2.0 | Alcohol consumption |
| | Ashkenazi Jewish heritage |
| | Early menarche (<12 years) |
| | Height (tall) |
| | High socioeconomic status |
| | Late age at first full-term pregnancy (>30 years) |
| | Late menopause (>55 years) |
| | No full-term pregnancies or never breastfed a child |
| | Obesity (postmenopausal)/adult weight gain |
| | One first-degree relative with breast cancer |
| | Personal history of endometrial, ovarian, or colon cancer |
| | Recent and long-term use of menopausal hormone therapy containing estrogen and progestin |
| | Recent oral contraceptive use |

American Cancer Society. Surveillance Research; 2011.
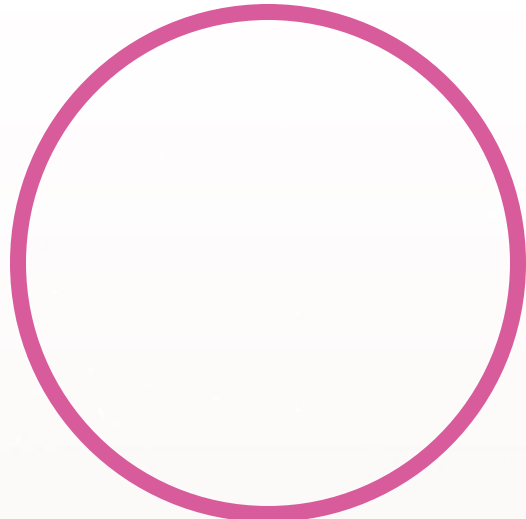
# *Atypical Hyperplasia*

- 1 million breast biopsies done in US annually: benign[1]
  - 10% have atypical hyperplasia

- Has some, but not all, features of cancer
  - "Premalignant" lesion

- Cannot use standard prediction models

- 5% by 10 years[2] and 30% by 25 years will have cancer
  - The younger the age at diagnosis, the higher the risk

- Usually not included as MRI candidates
  - Chemoprevention rarely taken

1. Hartmann LC, et al. *N Engl J Med*. 2015;372(1):78-89.
2. Menes TS, et al. *JAMA Oncol*. 2017;3(1):36-41.

# Alcohol and Breast Cancer: *Pooled Analysis of 322,647 Women Evaluated Up to 11 years*

- Consumers of 30-60 g/day**\*** of alcohol:
  - RR for breast cancer = 1.41
  - Not affected by BMI or HT

  **\*2.3-4.5 bottles of beer**
  **2.8-5.6 glasses of wine**
  **2.0-4.0 shots of hard liquor**

- Risk may be reduced by increased folate intake (≥ 600 μg/day)

1. Smith-Warner SA, et al. *JAMA*. 1998;279(7):535-540.
2. Zhang S, et al. *JAMA*. 1999;281(17):1632-1637.
3. Chen WY, et al. *JAMA*. 2011;306(17):1884-1890.
4. Scoccianti C, et al. *Am J Prev Med*. 2014;46(3 Suppl 1);S16-S25.

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# Menopausal Hormone Therapy: 20 Years Later Breast Cancer Incidence and Mortality: ET

- 20-year follow-up of 27,347 postmenopausal women in WHI
  - Mortality information available for >98%

- **CEE alone associated with lower breast cancer incidence and mortality**
  - HR = 0.78 (95% CI, 0.65-0.93) (incidence)
  - HR = 0.60 (95% CI, 0.37-0.97) (mortality)

- CEE-MDR higher incidence but no higher mortality
  - HR = 1.28 (CI 1.13-1.45); HR = 1.35 (CI 9.4-1.95)

Chlebowski RT, et al. *JAMA*. 2020;324(4):369-380.

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# *Factors Shown to Have No Effect on Risk of Breast Cancer*

- Breast augmentation
- Smoking
- Abortion
- Breast feeding < 1 year
- Fat intake
- Selenium in diet
- Caffeine
- Short-term postmenopausal hormone therapy (HT)

ACOG Committee Opinion No. 434. *Obstet Gynecol.* 2009;113(6):1417-1418.

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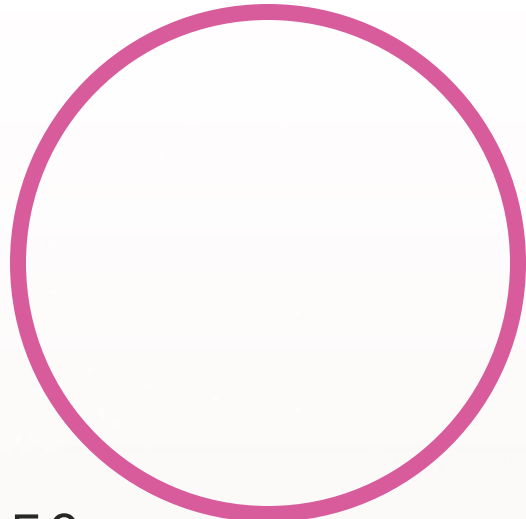
# BRCA Tumor Suppressor Gene Mutations

- More than 2,000 variants of BRCA1 and BRCA2 exist with variable penetrance
  - Increased risk of carcinoma of breast, ovary, pancreas, prostrate, and melanoma
- Lifetime risks

|  | BRCA1 | BRCA2 |
|---|---|---|
| Breast cancer | 65%-85% | 45%-85% |
| Ovarian cancer | 39%-46% | 10%-27% |

- 3%-20% of mutations are variants of unknown significance (VUS)

# Breast Cancer Incidence by Risk Status

- 1 in 8 average-risk women will develop breast cancer by age 80-90
- 1 in 3 high-risk women will develop breast cancer by age 50
- Testing to identify high-risk women expanding
  - Tests used to screen high-risk women now start earlier, are conducted more frequently, and involve more modalities
- Prevention in high-risk women often involves surgery

Blaes A, et al. *J Womens Health (Larchmt)*. 2020;29(5):686-692.

# *Average Risk for Breast Cancer*

- No personal history of breast cancer
- No confirmed or suspected genetic mutation known to increase risk of breast cancer
- No history of radiotherapy to the chest at a young age
- No significant family history of breast cancer
- No prior diagnosis of benign proliferative breast disease or worse
- No significant mammographic breast density

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# Breast Cancer Screening Recommendations for Average Risk

| | SBE | AGE | CBE | AGE | MAMMOGRAPHY |
|---|---|---|---|---|---|
| ACOG | Not recommended | 25-39 | May offer Q1-3 | 40-75 | May offer Q1-2 |
| | | 40 | May offer Q1 | | |
| ACS | Not recommended | | Not recommended | 40-75 | Recommend Q1-2 |
| ACR | | | | 40-75 | Recommend Q1 |
| USPSTF | Not recommended | | Insufficient evidence | 40-75 | Recommend Q2 |

1. ACOG Practice Bulletin No. 179. *Obstet Gynecol.* 2017;130(1):e1-e16.
2. Siu AL, et al. *Ann Intern Med.* 2016;164(4):279-296.
3. USPSTF, Nicholson WK, et al. *JAMA.* 2024;331(22):1918-1930.

*Women's Health* 2024 | *Beyond the Annual Visit*
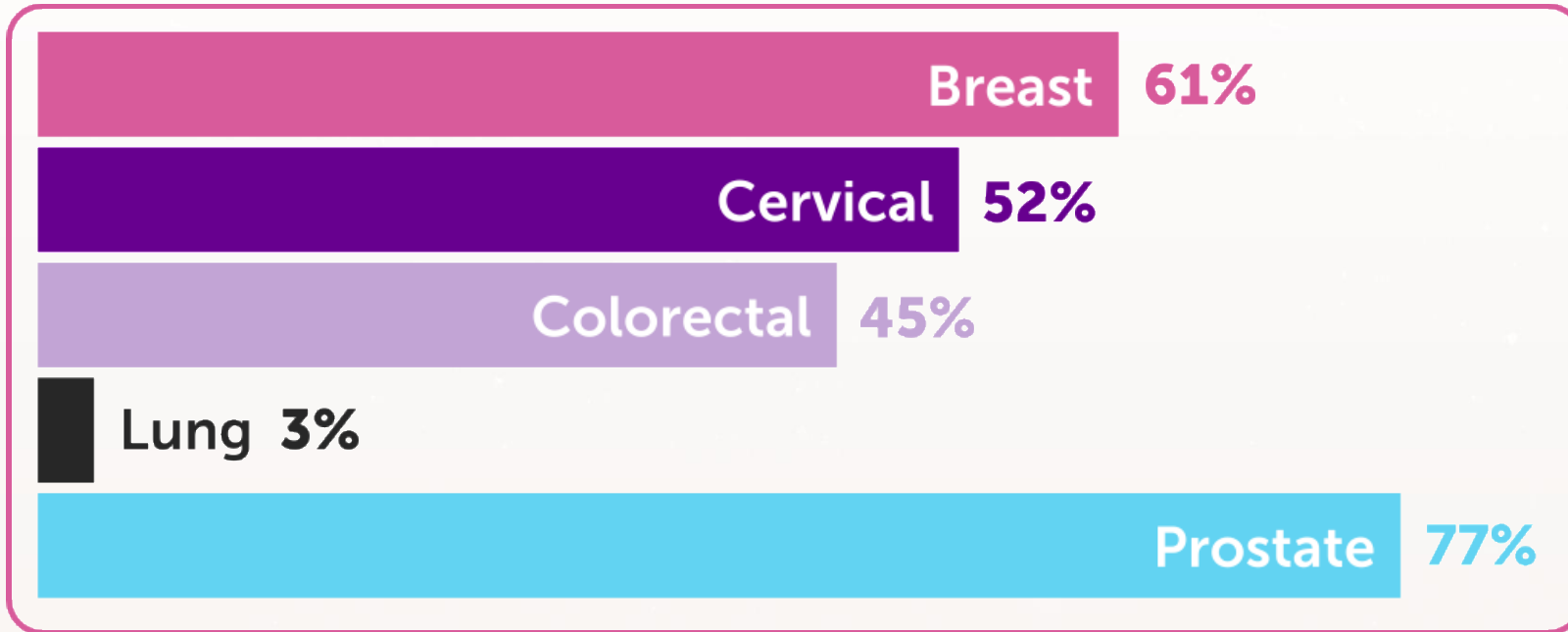
# *Shanghai SBE Trial*

- Initial instruction, reinforcement lessons at 1 & 3 years
- SBE practice under medical supervision every 6 months for 5 years
- Ongoing reminders to practice monthly
- 1989-1991 instructions followed for morbidity to 2000

| | BSE | Control | SRR (95% CI) |
|---|---|---|---|
| **Number** | 132,979 | 133,085 | |
| **Cancer deaths** | 135 | 131 | 1.04 (0.82-1.33) |
| **Benign lesions** | 2,387 | 1,296 | |

Cummings SR, et al. *JAMA.* 1999;281(23):2189-2197.

# *Clinical Breast Examination Limitations*

- Physicians who were tested on artificial models detected:
  - 44% of lumps
  - 87% of 1-cm masses
  - 33% of 0.5-cm masses
  - 14% of 0.3-cm masses
  - 50% of hard masses
  - 36%-40% of soft masses
  - 44% of deep or medium-depth masses
- Easier to detect if larger, firmer, more superficial

# Percent of Cancers Detected by Screening, by Cancer Type

Breast 61%

Cervical 52%

Colorectal 45%

Lung 3%

Prostate 77%

10% increase in screenings would reduce breast cancer deaths 82/100,000*

*Knudsen AB, et al. *JAMA Netw Open*. 2023;6(11):e2344698.

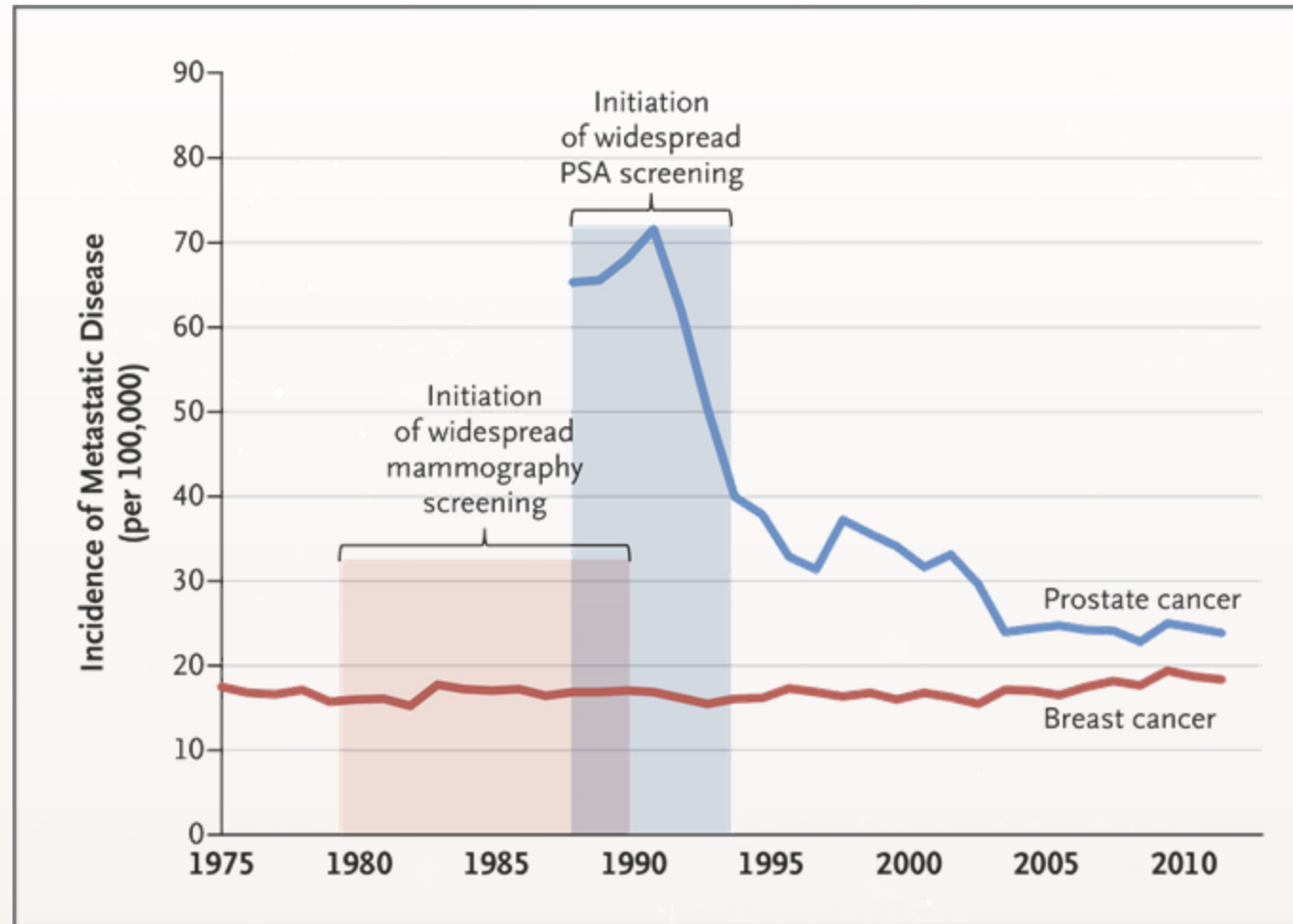Women's Health 2024 | *Beyond the Annual Visit*

# *Mammography Screening Reduces Rates of Advanced & Fatal Breast Cancer*

- 549,091 Swedish women aged 40-69 years
  - Screening age study frequency
    - 40-54 Q 18 months
    - 55-69 Q 24 months

- Women who had mammography screening had statistically significant results
  - 25% reduction in rate of advanced breast cancer at time of diagnosis
  - 49% reduction in dying of breast cancer in 10 years

- Conclusion: those changes appeared to be independent of recent changes in treatment regimen

Duffy SW, et al. *Cancer.* 2020;126(13):2971-2979.

# Incidence Over Time of Cancer Metastatic at First Presentation



Welch HG, et al. *N Engl J Med*. 2015;373(18):1685-1687.

# *Harms of Mammography Screening*

- False positive results
  - Need for additional screening, biopsy
- Overdiagnosis
- Detection and treatment of invasive and noninvasive cancer that would never have been detected or threaten health in the absence of screening
  - Overtreatment

USPSTF, Nicholson WK, et al. *JAMA*. 2024;331(22):1918-1930.

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# *USPSTF Comment on Mammographic Tests*

- Both digital mammograph (2D) and digital breast tomosynthesis (3D) are effective mammographic screening modalities

- Small increase seen in positive predictive value of 3D over 2D

- No statistically significant difference seen in interval breast cancer detection or in tumor characteristics when comparing 3D to 2D between screening intervals

- Similar benefits and fewer false positives with 3D vs 2D

- Inconclusive evidence available

1. USPSTF, Nicholson WK, et al. *JAMA*. 2024;331(22):1918-1930.
2. Henderson JT, et al. *JAMA*. 2024;331(22):1931-1946.

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# BI-RADS Breast Density Categories

| BI-RADS Category | Description | % Population | Mammogram Sensitivity |
|:---:|:---|:---:|:---:|
| 1 | Almost entirely fat | 10% | 88 |
| 2 | Scattered fibroglandular densities | 43% | 82 |
| 3 | Heterogeneously dense | 39% | 69 |
| 4 | Extremely dense | 8% | 62 |

ACOG Committee Opinion No. 625. *Obstet Gynecol.* 2015;125(3):750-751.
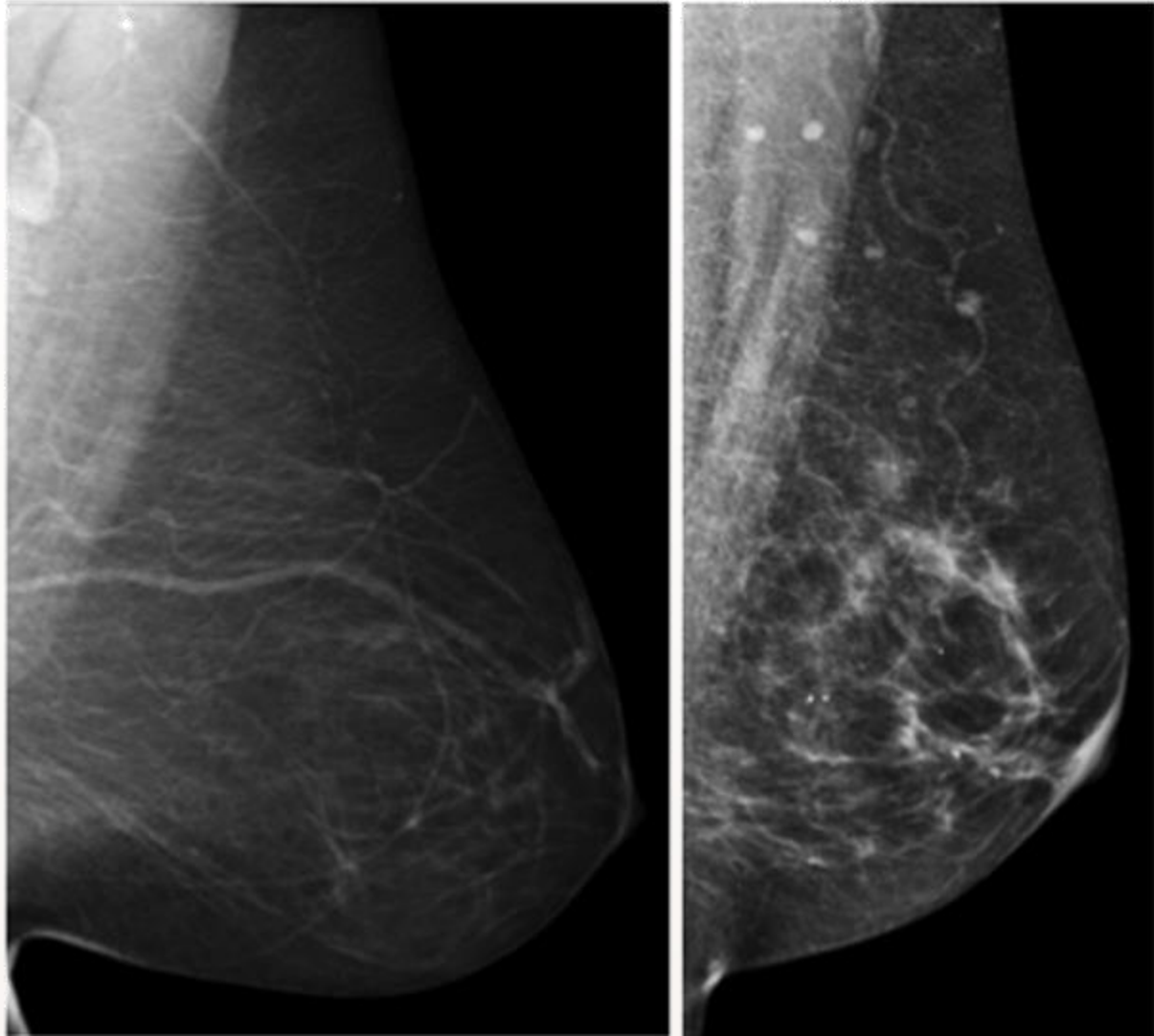
Almost Entirely Fat | Scattered Areas

Nondense
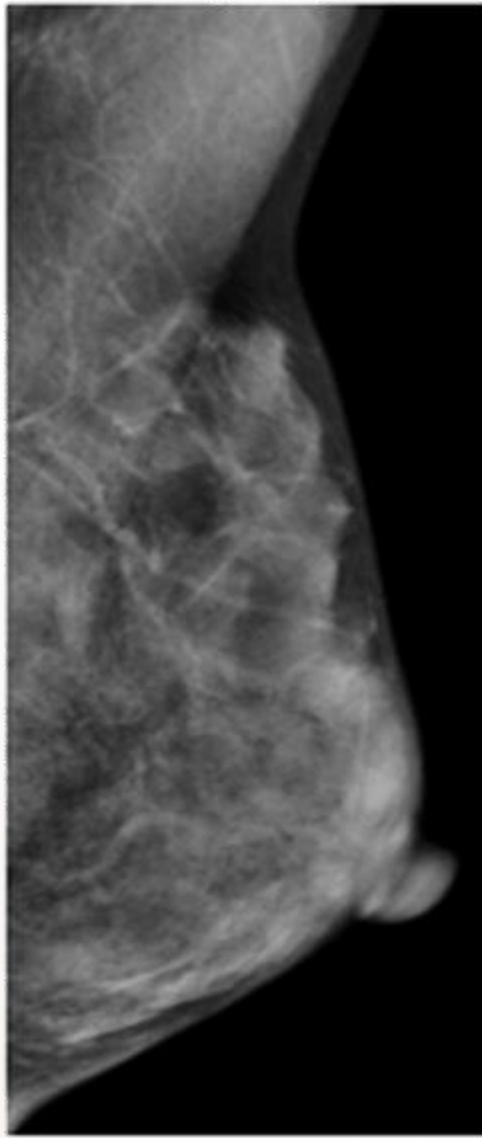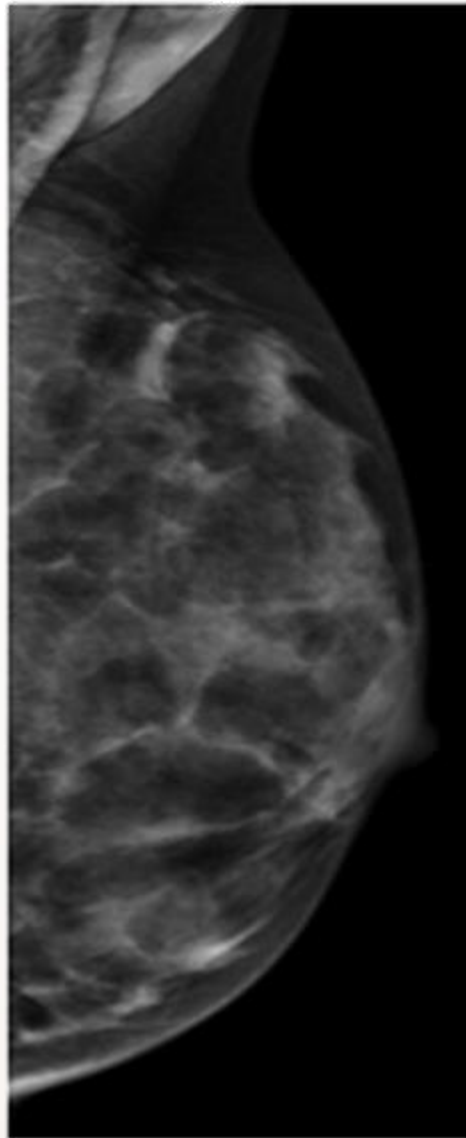
Heterogeneously Dense

Extremely Dense

Dense

# *USPSTF Position: Dense Breasts*

- Current evidence is insufficient to assess the balance of benefits and harms of supplemental screening for breast cancer using breast ultrasonography or MRI in women identified to have dense breasts on an otherwise negative screening mammogram

- Increased breast density **not** associated with higher breast cancer mortality after adjustments

## BUT

USPSTF, Nicholson WK, et al. *JAMA*. 2024;331(22):1918-1930.

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# *Breast Density Reporting Laws*

- Most states have various laws regarding follow-up needed for women with mammographic "dense breasts"
  - Breasts > 50% fibroglandular tissue
    - 40%-50% of all women

- Require that clinician inform woman that she has dense breasts and educate her about:
  - Increased risk of breast cancer
  - Supplemental screening for early breast cancer

- Some states require physicians to offer supplemental whole-breast ultrasonography, independent of her other risk factors

Slanetz PJ, et al. *N Engl J Med*. 2015;372(7):593-595.
ACOG Committee Opinion No. 625. *Obstet Gynecol*. 2015;125(3):750-751.

# MD Knowledge, Attitudes, and Practices Regarding Breast Density

- 155 MD responses
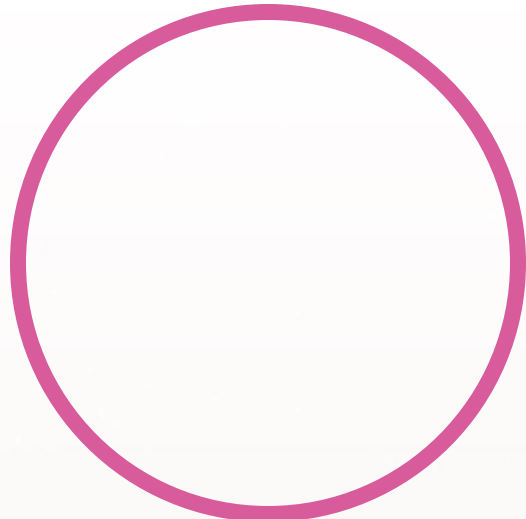  - 62% not aware of increased risk with dense breasts
    - 83% PCPs vs 44% specialists
  - 48% did not know their state's law
    - 68% PCPs vs 29% specialists

- ≥35 states have enacted breast density informational laws
  - US lower cost, widely available, lower sensitivity than MRI
  - MRI requires contrast injection, more costly

Brown J, et al. *J Womens Health (Larchmt)*. 2019;28(9):1193-1199.

# What *Should* We Be Doing for *Average-Risk* Women?

- Stop screening women with no benefit[1]
  - 48% of primary care physicians said they would recommend breast cancer screening for women diagnosed with terminal lung cancer

- Calculate patient's individual breast cancer risk[2]
  - Use estimate to determine screening frequency and modality
  - Low accuracy in predicting probability of breast cancer in individuals[3]

- Provide chemoprevention or other interventions for moderate-risk patients when 5-year risk >3%[4]

1. Leach CR, et al. *Cancer*. 2012;118(1):27-37.
2. Saini SD, et al. *JAMA*. 2014;312(21):2211-2212.
3. Nelson HD, et al. *JAMA* 2019;322(9):868-886.
4. US Preventive Task Force. Draft rec. May 2023.

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# *Prevention Strategies: Healthy Lifestyle*

- 23% of breast cancer cases in UK thought to be preventable

- Cancer Research UK: factors to reduce risk[1]
  - Healthy weight reduced risk 13.9%
    - Obesity accounts for 8%
  - Regular exercise reduced risk 12.2%
  - ≤ 3 alcohol/week reduced risk 10.7%
    - EtOH accounts for 8%
  - Avoiding HT reduced risk 22.9%

- Unhealthy lifestyle increases more than genetic risk[2]

1. Cancer Research UK. Accessed 7/12/24.
https://www.cancerresearchuk.org/health-professional/cancer
statistics/statistics-by-cancer-type/breast-cancer
2. Al Ajmi K, et al. *JAMA Netw Open*. 2020;3(4):e203760.

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# Calculators for Risk Assessment for the General Population to Identify Moderate Risk

- Apps in breast cancer risk calculators

- Breast Cancer Surveillance Consortium (BCSC) Risk Calculator[1]
  - https://tools.bcsc-scc.ucdavis.edu/BC5yearRisk

- Breast Cancer Risk calculator[2]
  - https://bcrisktool.cancer.gov/

- Tyrer-Cuzick (IBIS) calculator[3]
  - https://ibis-risk-calculator.magview.com/
    - Most detailed for MRI screening; includes BMI, breast density, BRCA mutations

1. Shieh Y, et al. *JAMA*. 2020;324(3):291-292.
2. Nelson HD, et al. *JAMA*. 2019;322(9):868-886.
3. Pearlman MD. *OBG Mgmt*. 2023;35(2):33.

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# *Breast Cancer Risk Assessment Tool: Typical Questions*

- Calculate risk for next 5 years and lifetime
  - Q1: History of DCIS or LCIS?
  - Q2: Current age?
  - Q3: Age at time of first menstrual period?
  - Q4: Age at time of first birth?
  - Q5: No. of 1st degree relatives with breast cancer?
  - Q6: Number of breast biopsies?
    - Any atypical hyperplasia?
  - Q7: Race/ethnicity?

Available at: http://www.cancer.gov/bcrisktool/

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# USPSTF Draft Recommendation 2019

**Draft: Recommendation Summary**

| Population | Recommendation | Grade (What's This?) |
|---|---|---|
| Women at increased risk for breast cancer | The USPSTF recommends that clinicians offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, to women who are at increased risk for breast cancer and at low risk for adverse medication effects. | B |
| Women not at increased risk for breast cancer | The USPSTF recommends against the routine use of risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors, in women who are not at increased risk for breast cancer. | D |

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# *Breast Cancer Risk Reduction Agents for Moderate-Risk Women (>3% in 5 Years)*

- Standard SERMS: Tamoxifen 20 mg and raloxifene 60 mg daily for 5-10 years
  - Tamoxifen also reduces risk of DCIS

- Newer SERMS for osteoporosis and breast cancer reduction(?)
  - Lasofoxifene, bazedoxifene, ospemifene

- Aromatase inhibitors (off-label)
  - Exemestane 25 mg, **anastrozole 1 mg**, letrozole 2.5 mg

# Medication for Primary Reduction of Breast Cancer

- 46 studies (82 articles), >5 million women

- Placebo-controlled trial, relative risk for invasive cancer
  - Tamoxifen                                       0.69 (95% CI, 0.59-0.84)
  - Raloxifene                                       0.44 (95% CI, 0.24-0.80)
  - Aromatase inhibitors*                     0.45 (95% CI, 0.26-0.70)

- Other benefits
  - Raloxifene: lower risk of vertebral fractures (0.61)
  - Tamoxifen: lower risk of nonvertebral fractures (0.66)

- Risk: tamoxifen > raloxifene ↑ VTE

- Risk: tamoxifen increased endometrial cancer and cataracts

- *Exemestane and anastrozole

Nelson HD, et al *JAMA*. 2019;322(9):868-886.

# *Significant Underutilization of Chemoprevention for Breast Cancer*

- >10 million women eligible
- 2016 meta-analysis of uptake: 8.7% of "eligibles"
- High uptake: abnormal biopsy results, physician recommendation, older age
- Barriers:
  - Complexity of risk-associated models
  - Need to counsel about benefits and risk
  - Lack of information for non-Caucasian women
  - Distrust of medical community

Daly MB, et al. *JAMA Oncol.* 2019;5(11):1542-1544.
Nelson HD, et al *JAMA.* 2019;322(9):868-886.

# Preventing Breast Cancer: What We Know Works Now

| Health Messages | Risk Group | Approximate % of US Female Population Aged <50 Years Affected, % | Possible Reduction in Risk, % | Time Until Benefit, y |
|---|---|---|---|---|
| **Premenopausal women** | | | | |
| Alcohol intake: None | Youth (ages 12-17y), drinking at least one drink in past 30/d | 13 | 20-30 | 10-20 |
| Alcohol intake: ≤1 serving/d | Young adults (ages 18-24y) drinking ≥4 drinks/wk | 15 | 20-30 | 10-20 |
| Healthy weight: Avoid weight gain | All women | 13 | 25 | 10-20 |
| Physical activity: ≥30 min/d | Women not meeting physical activity guidelines | 54 | 20 | 10-30 |

Colditz GA, et al. *CA Cancer J Clin*. 2014;64(3):186-194.

# *Preventing Breast Cancer: What We Know Works Now*

| Health Messages | Risk Group | Approximate % of US Female Population Aged <50 Years Affected, % | Possible Reduction in Risk, % | Time Until Benefit, y |
|---|---|---|---|---|
| **Premenopausal women** | | | | |
| Healthy diet: Fruits, vegetables & whole grains | Youth eating very few fruits & vegetables | 5-11 | 20-50 | 5-20 |
| Breastfeed: 1y total across all children | Women who have given birth | 81 | 18 | 5 |
| Prophylactic bilateral oophorectomy | BRCA1 and 2 carriers | <1 | 50 | ≥2 |
| Tamoxifen | High-risk women aged ≥35y (greater than or equal to the risk for average woman aged 60y) | 3 | 50 | 2 |

Colditz GA, et al. *CA Cancer J Clin*. 2014;64(3):186-194.

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# Preventing Breast Cancer: What We Know Works Now

| Health Messages | Risk Group | Approximate % of US Female Population Aged <50 Years Affected, % | Possible Reduction in Risk, % | Time Until Benefit, y |
|---|---|---|---|---|
| **Postmenopausal women** | | | | |
| Alcohol intake: Serving/d | Adults drinking ≥4 drinks/wk | 13 | 35 | 5-10 |
| Healthy weight: Weight loss | Overweight and obese (eg 5'4" and >145 lbs) | 64 | 50 | 2-5 |
| Physical activity: ≥30 min/d | Women not meeting physical activity guidelines | 54 | 20 | 10-20 |
| Estrogen-plus-progestin postmenopausal hormones: Avoid | Current users | 1.7 | 10 | 1 |
| Tamoxifen and raloxifene | High-risk women (greater than or equal to the risk for an average woman aged 60y) | 30 | 50 | 2 |

Colditz GA, et al. *CA Cancer J Clin*. 2014;64(3):186-194.

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# *Conclusions*

- Breast cancer incidence is increasing but mortality is decreasing, as are the disparities between groups

- Screening recommendations are beginning to converge
  - For average-risk patients, SBE and CBE are not helpful
  - Mammography starts at age 40 and continues until risks outweigh benefits

- Be aware of state laws for follow-up of mammographic finding of dense breasts

- Calculate interval and lifetime breast cancer risks starting at age 35

- Focus on breast cancer prevention with healthier lifestyle for all and chemoprevention for moderate-risk patients