Breast Cancer Updates and Hormone Replacement Therapy

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•“Cancer begins and ends with people. In the midst of scientific abstraction, it is sometimes possible to forget this one basic fact. Doctors treat diseases but they also treat people, and this precondition of their professional existence sometimes pulls them in two directions at once.”
~June Goodfield

Objectives

1. Review breast cancer statistics

2. Key principles in the multidisciplinary breast cancer management.

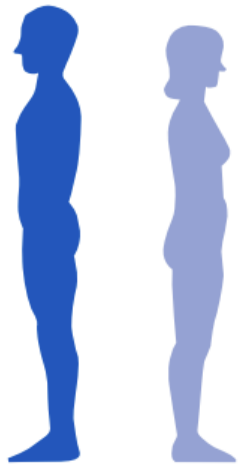
3. Hormone replacement therapy and the Women's Health Initiative Trials.

4. Research trends

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2024 Estimates

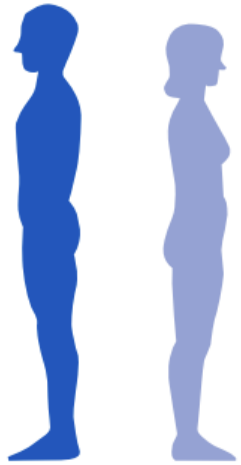
Estimated New Cases

Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	**1,029,080**		**All sites**	**972,060**	



Estimated Deaths

Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
Prostate	35,250	11%	Breast	42,250	15%
Colon & rectum	28,700	9%	Pancreas	24,480	8%
Pancreas	27,270	8%	Colon & rectum	24,310	8%
Liver & intrahepatic bile duct	19,120	6%	Uterine corpus	13,250	5%
Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
Urinary bladder	12,290	4%	Leukemia	10,030	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	**322,800**		**All sites**	**288,920**	



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

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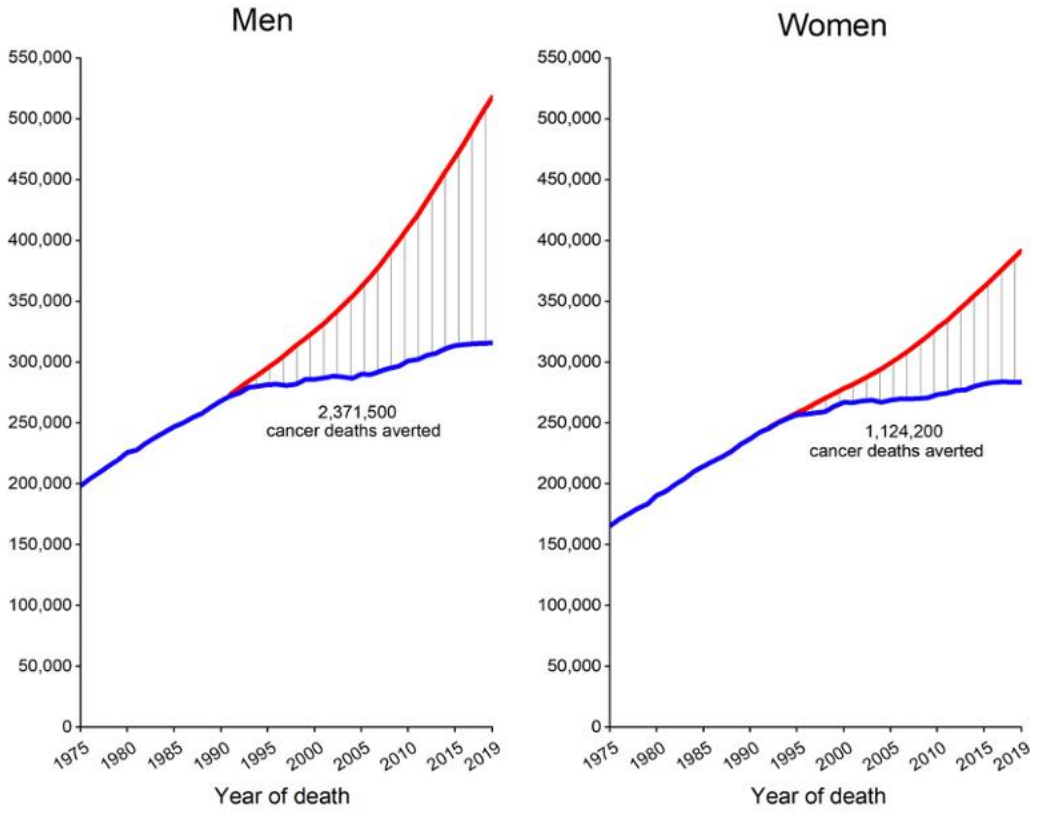


- Breast cancer mortality peaked in 1989 and has since decreased by 42%.
- Awareness and screening.
- Improvements treatment.

Total Number of Cancer Deaths Averted During 1991-2019 in Men and 1992-2019 in Women, United States. The blue line represents the actual number of cancer deaths recorded in each year; the red line represents the number of cancer deaths that would have been expected if cancer death rates had remained at their peak.

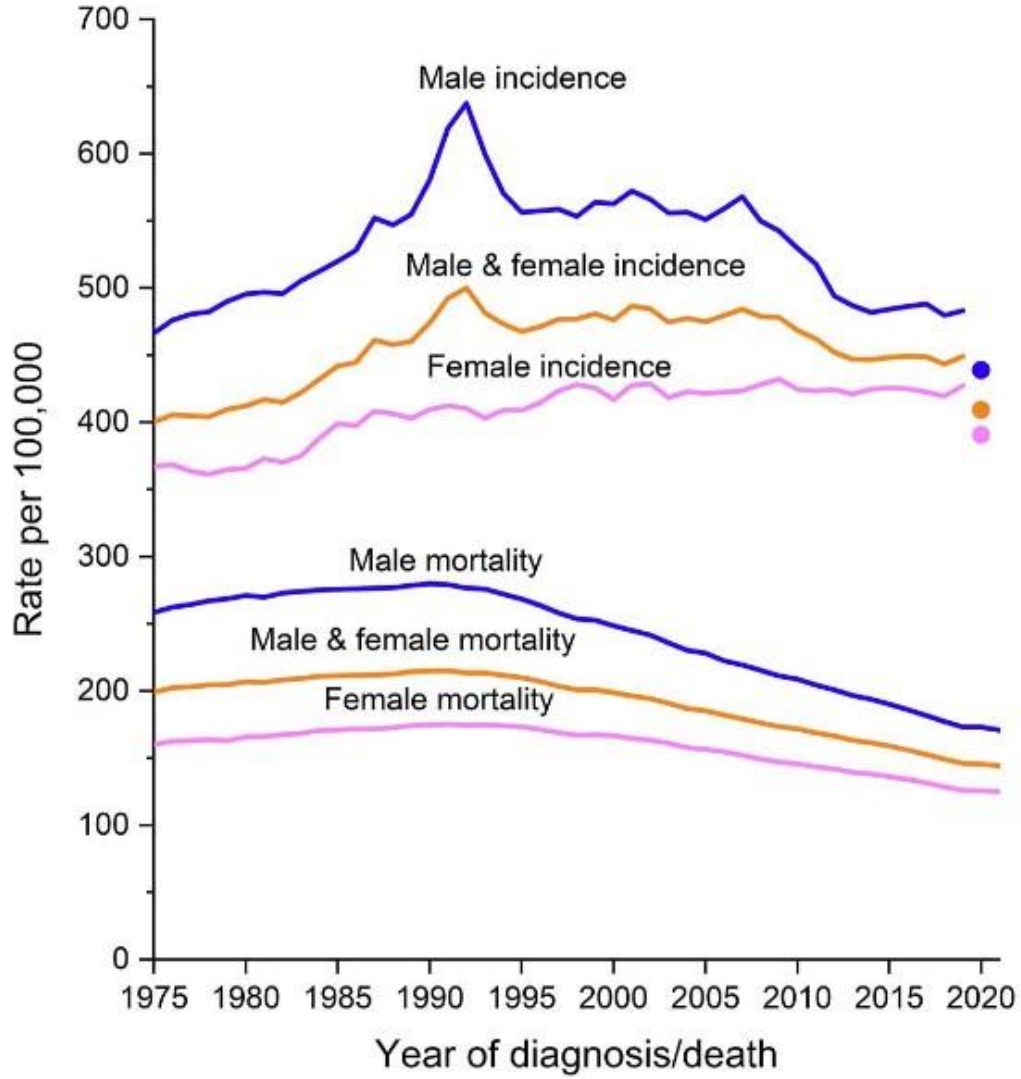


FIGURE 2 Trends in cancer incidence (1975–2020) and mortality (1975–2021) rates by sex, United States. Rates are age adjusted to the 2000 US standard population. Incidence rates are also adjusted for delays in reporting. Incidence data for 2020 are shown separate from trend lines.

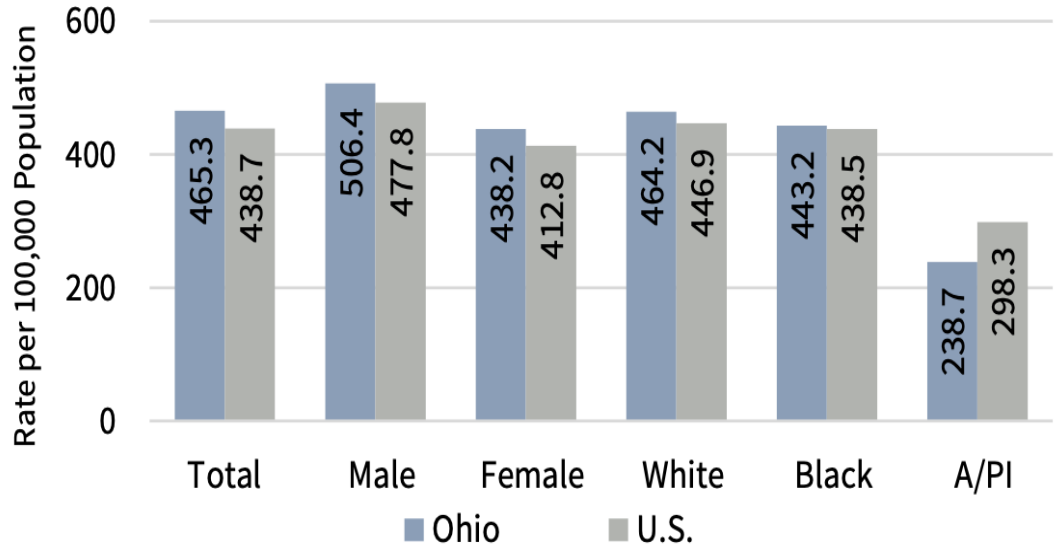
TABLE 10 Five leading causes of cancer death in the United States by age and sex, 2021.

Ranking	All ages	Birth to 19 years	20–39 years	40–49 years	50–64 years	65–79 years	80 years and older
Male							
All sites	318,670	1015	3927	8361	68,503	146,904	89,956
1	Lung & bronchus	Brain & ONS	Colon & rectum	Colon & rectum	Lung & bronchus	Lung & bronchus	Lung & bronchus
	71,549	292	[illegible]	[illegible]	15,950	71,548	17,157
2	Prostate	Leukemia	Brain & ONS	Lung & bronchus	Colon & rectum	Prostate	Prostate
	32,563	257	531	1004	7866	32,563	15,794
3	Colon & rectum	Bones & joints	Leukemia	Brain & ONS	Pancreas	Pancreas	Colon & rectum
	28,370	117	422	695	6132	28,370	7043
4	Pancreas	Soft tissue[a]	Testis	Pancreas	Liver[b]	Colon & rectum	Urinary bladder
	24,912	88	230	649	4239	24,912	5821
5	Liver[b]	NHL	NHL	Esophagus	Esophagus	Liver[b]	Pancreas
	18,828	38	197	420	3559	18,827	5558
Female							
All sites	286,543	707	4530	10,488	61,321	121,051	88,443
1	Lung & bronchus	Brain & ONS	Breast	Breast	Lung & bronchus	Lung & bronchus	Lung & bronchus
	62,955	211	1076	2782	13,451	30,723	17,743
2	Breast	Leukemia	Uterine cervix	Colon & rectum	Breast	Breast	Breast
	42,310	138	506	[illegible]	10,898	15,739	11,813
3	Colon & rectum	Bones & joints	Colon & rectum	Lung & bronchus	Colon & rectum	Pancreas	Colon & rectum
	24,361	85	415	896	5200	10,759	8990
4	Pancreas	Soft tissue[a]	Brain & ONS	Uterine cervix	Pancreas	Colon & rectum	Pancreas
	22,994	79	362	798	4386	8560	7304
5	Ovary	Kidney[c]	Leukemia	Ovary	Ovary	Ovary	Leukemia
	13,430	25	310	544	3439	6017	4048

Ohio Department of Health

New Cancer Cases

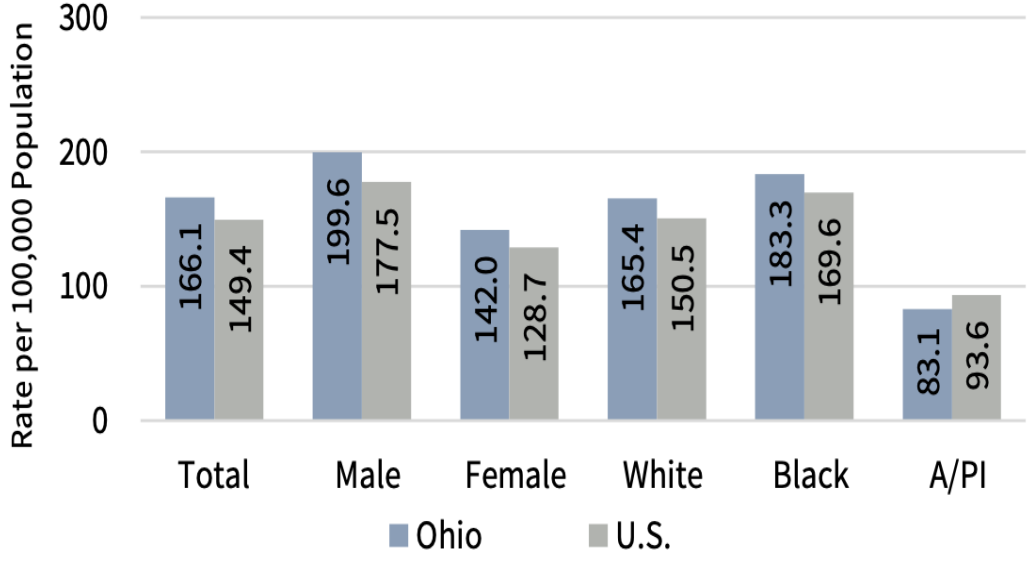
Figure 1. Average Annual Age-Adjusted Cancer Incidence Rates by Sex and Race in Ohio and the United States, 2016-2020



Source: Ohio Cancer Incidence Surveillance System, Ohio Department of Health, 2023; Surveillance, Epidemiology, and End Results Program, National Cancer Institute, 2023.
Rates are per 100,000 population and age-adjusted to the 2000 U.S. standard population.
A/PI = Asian/Pacific Islander.

Cancer Deaths

Figure 2. Average Annual Age-Adjusted Cancer Mortality Rates by Sex and Race in Ohio and the United States, 2016-2020

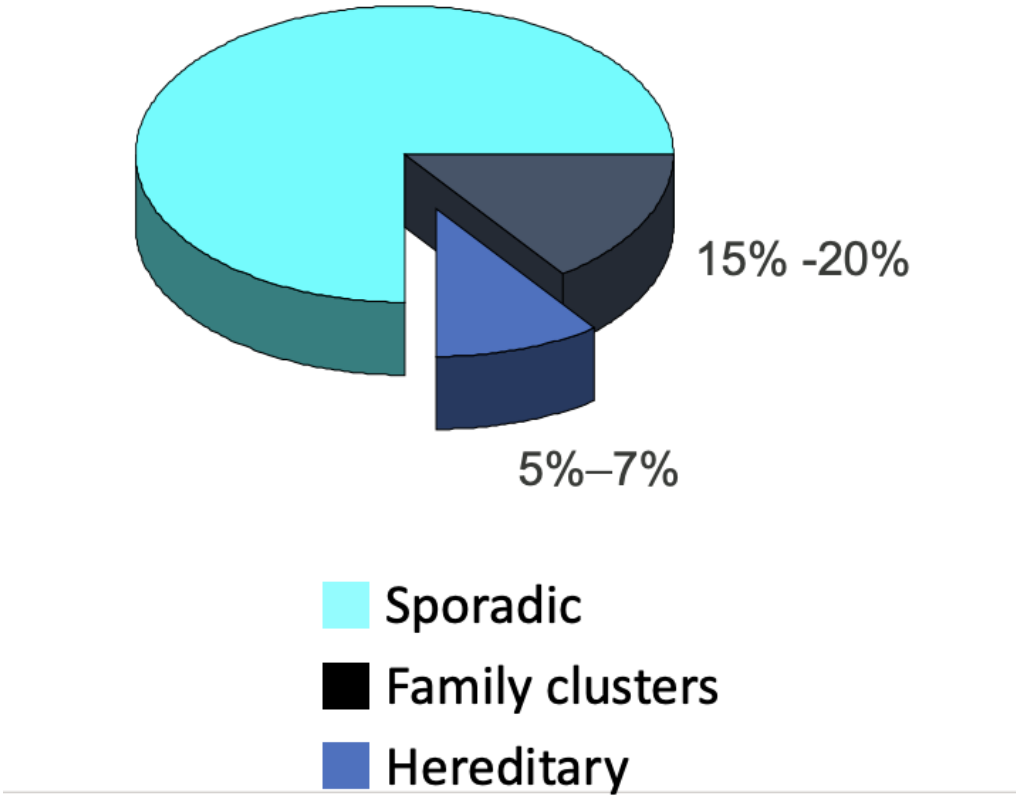


Source: Bureau of Vital Statistics, Ohio Department of Health, 2023; Surveillance, Epidemiology, and End Results Program, National Cancer Institute, 2023.
Rates are per 100,000 population and age-adjusted to the 2000 U.S. standard population.
A/PI = Asian/Pacific Islander.

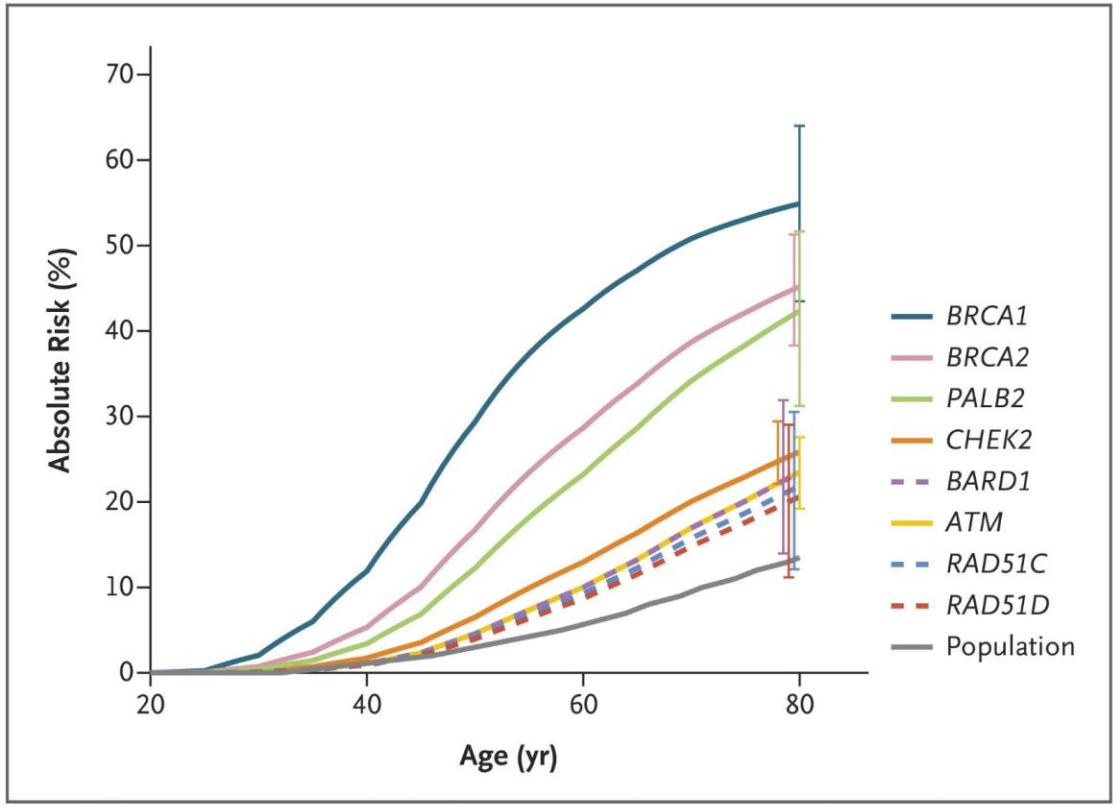
Screening Recommendations

	USPSTF (2024)	ACS (2023)	ACR (2023)	NCCN (2024)	ACOG (2017)
Start Age	Age 40.	Age 40–44: Women have the option for annual screening.	Annual risk assessment by age 25. All women at average risk should start annual mammography by age 40.	Age 40: Annual mammogram with tomosynthesis.	Age 40: Offer screening mammography. Start no later than age 50.
Interval	Biennial (every 2 years) for women aged 40–74.	Age 45–54: Annual mammograms. Age 55+: Annual or biennial.	Annual for women of average risk.	Annual for women of average risk.	Every 1–2 years, based on shared decision-making.
Stop Age	Recommends screening for women up to age 74. Evidence is insufficient to determine benefit for women 75 and older.	Continues as long as a woman is in good health and has at least a 10-year life expectancy.	Continues as long as a woman has at least a 5–7-year life expectancy.	Continues as long as a woman has at least a 10-year life expectancy.	Continue until at least age 75. Decisions past age 75 should be based on shared decision-making.
High-Risk Patients	Recommends risk assessment with a brief familial risk tool.	Recommends annual MRI and mammogram starting at age 30 for high-risk women.	Recommends MRI surveillance for high-risk women starting at ages 25–30, plus annual mammography.	Annual mammogram plus annual breast MRI for high-risk women.	More frequent exams and/or earlier screening is needed.

How Much Breast Cancer Is Hereditary?



Breast Cancer Risk



Breast Cancer Association Consortium N Engl J Med 2021

High Penetrance Breast Cancer Genes

Gene	Risk Level (estimated absolute lifetime risk)	Recommended Screening	Preventive Mastectomy?
TP53	High (>60%)	MRI at 20, +/- mammogram at 30	Yes, discuss
BRCA1	High (>60%); predisposed to TNBC	MRI at 25, mammogram at 30	Yes, discuss
BRCA2	High (>60%); predisposed to ER-positive	MRI at 25, mammogram at 30	Yes, discuss
PALB2	High (40-60%)	MRI and mammogram at 30	Yes, discuss
PTEN	High (40-60%)	MRI and mammogram at 35	Yes, discuss
CDH1	High (40-60%); predisposed to lobular	MRI and mammogram at 30	Yes, discuss
STK11	High (35-55%)	MRI and mammogram at 30	Yes, discuss
ATM	Moderate (20-40%); predisposed to ER-positive	MRI at 30-35, mammogram at 40	Insufficient evidence
CHEK2	Moderate (20-40%); predisposed to ER-positive	MRI at 30-35, mammogram at 40	Insufficient evidence
NF1	Moderate (20-40%)	MRI and mammogram, 30-50	Insufficient evidence
BARD1	Moderate (20-40%); predisposed to TNBC	MRI and mammogram at 40	Insufficient evidence
RAD51C	Moderate (20-40%); predisposed to ER-negative	MRI and mammogram at 40	Insufficient evidence
RAD51D	Moderate (20-40%); predisposed to ER-negative	MRI and mammogram at 40	Insufficient evidence

Risk Reduction

Surgical

- Bilateral prophylactic mastectomy high penetrance variants.
  - 95% Reduction in lifetime risk.

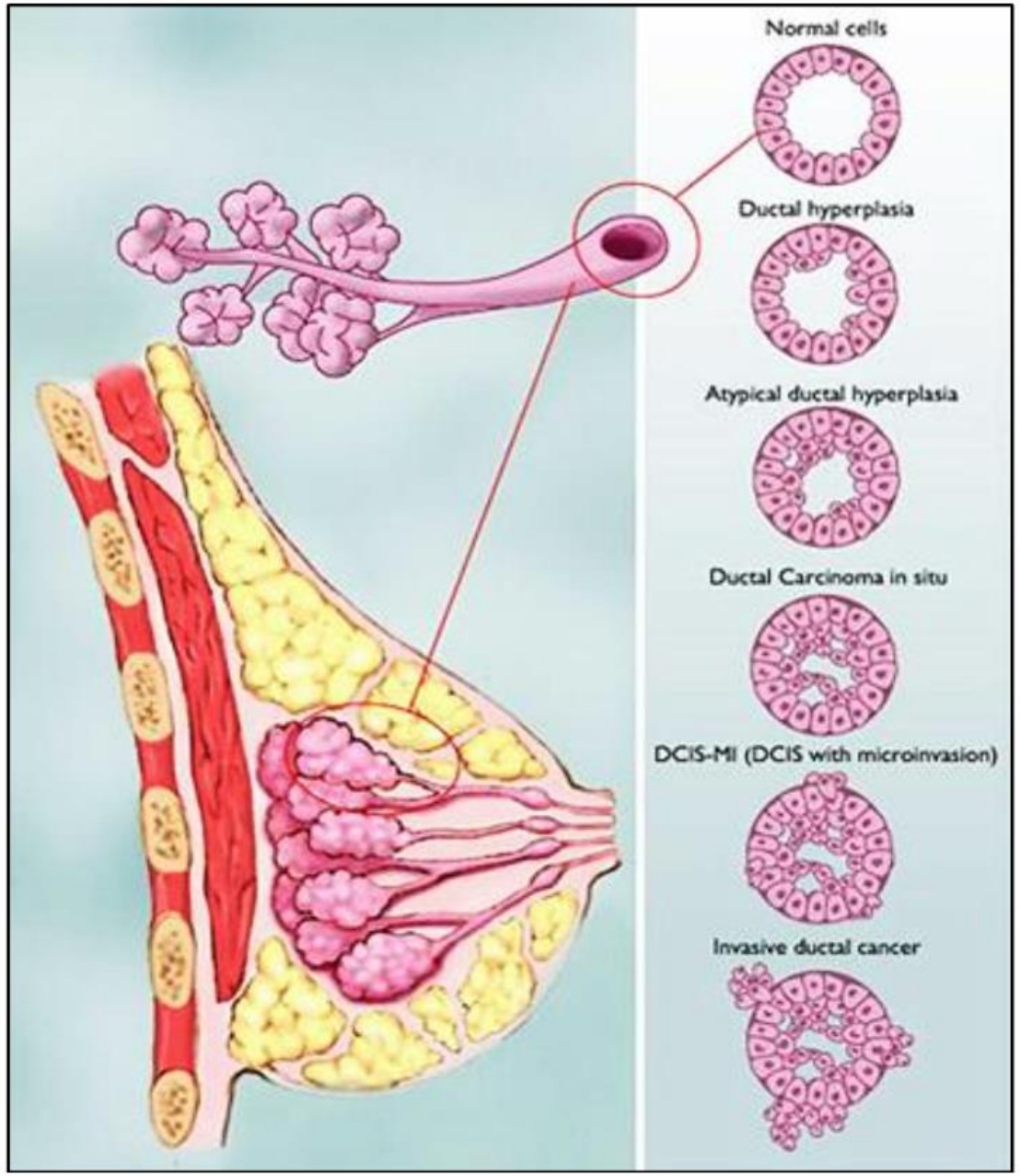
- *BRCA1/2* variants elevated risk for ovarian cancer (39%-58% for *BRCA1* and 13%-29% for *BRCA2*).
  - Risk-reducing bilateral salpingo-oophrectomy.
  - *BRCA1* -between ages 35-40
  - *BRCA2*-between ages 40-45

Nonoperative

- Endocrine therapy: selective estrogen receptor modulators (eg, tamoxifen or raloxifene) for 5 years,
  - 20-50% Reduction in lifetime risk

Types of Breast Cancer

1. Ductal
   - Ductal carcinoma in situ (DCIS)
   - Invasive ductal carcinoma (80%)
2. Lobular
   - Lobular carcinoma in situ (LCIS)
   - Invasive lobular carcinoma



Cancer Stage and Pathologic Grade

Stage	5-year Relative Survival Rate
0	100%
I	100%
II	93%
III	72%
IV	22%

Stage of Tumor	Size of the Cancer	Cancer in Lymph Nodes?	Metastasis
I	< 2 cm	None	None
II	2 - 5 cm	No, or yes on same side of breast	None
III	> 5 cm	yes, on same side of breast	None
IV	Any T	Any N	Yes

American Joint Commission Cancer- 8th

Breast Prognostic Staging: New Paradigm for 8th Edition Based on Outcomes of Treated Patients

- Two major databases with complete data:

T, N, M, Grade, HER2, ER, PR

  - MD Anderson Cancer Center (E. Mittendorf)
  - National Cancer Data Base (DJ Winchester)

- Prognostic Staging based on survival in patients who received treatment

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB

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Major changes in Stage Groups from Anatomic Staging for Many Situations - Examples

TNM			Biomarkers				Genomic Profile	Stage Groups	
T	N	M	Grade	HER2	ER	PR	Oncotype Dx	7th Edition Anatomic	8th Edition Prognostic
1	0	0	1	Neg	Neg	Neg	N/A	IA	IIA
3	1-2	0	1	Pos	Pos	Pos	N/A	IIIA	IB
0-2	2	0	1-2	Pos	Pos	Pos	N/A	IIIA	IB
2	0	0	Any	Neg	Pos	Any	< 11	IIA	IA

Treatment

Surgery

↓

Chemotherapy

↓

Radiation

↓

Anti-hormonal treatment

Removing source

↓

Systemic control

↓

Local control

↓

Keep cancer quiescent

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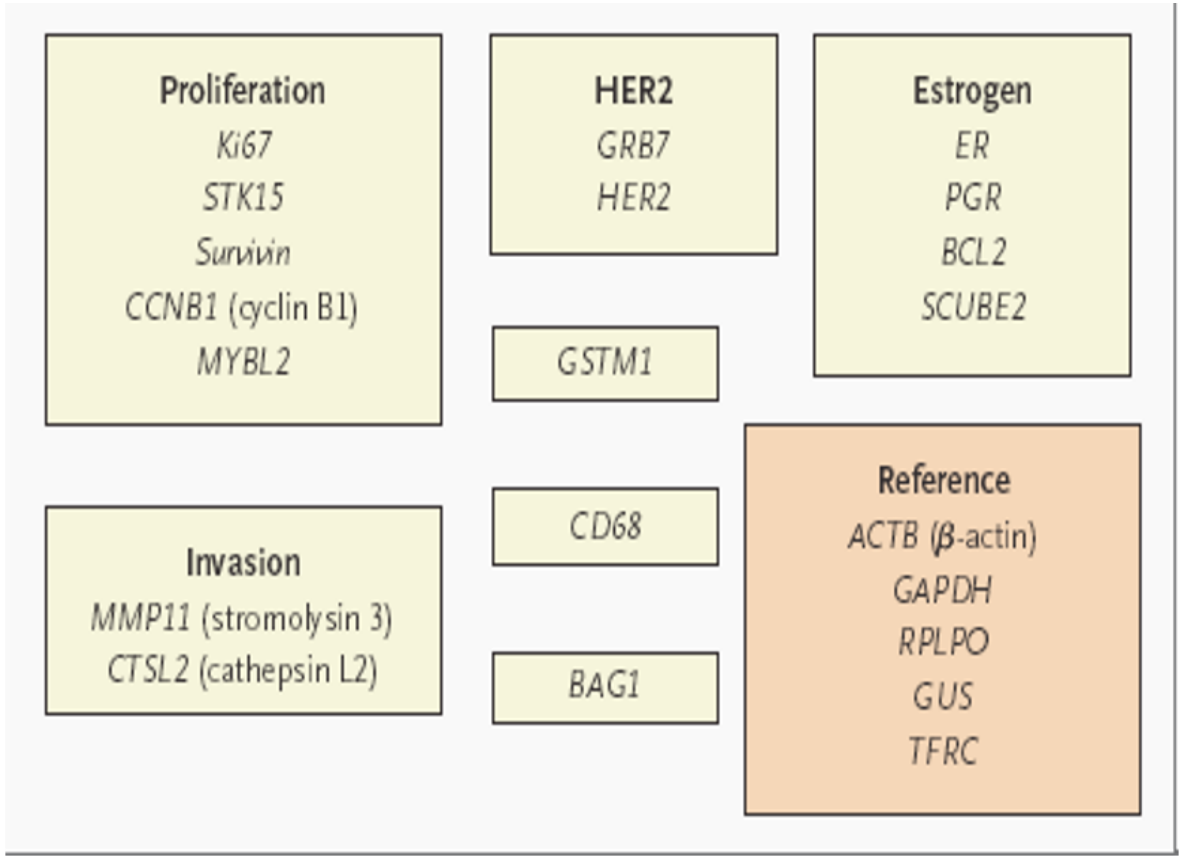
First Line Treatment

- Luminal-A: 70% (ER+/HER2-),
  - Treatment: Surgery
- Luminal-B: 10-15%, (ER+/HER2-)
  - Treatment: Start neoadjuvant chemotherapy, followed by surgery.
- Basal-Triple-negative: 10-15%
  - Treatment: Start neoadjuvant chemotherapy, followed by surgery.
- HER2-positive tumors: 5-10%
  - Treatment: Start HER2neu directed neoadjuvant chemotherapy, followed by surgery.

Trial Assigning Individualized Options for Treatment (Rx) (TAILORx trial)

- The landmark trial gave an evidence-based answer to the question of which women with this type of breast cancer may benefit from chemotherapy as a potentially life-saving treatment—and which may effectively pursue endocrine therapy (ET) alone and avoid the unnecessary side effects of chemotherapy.

Oncotype DX
21-gene recurrence-score assay



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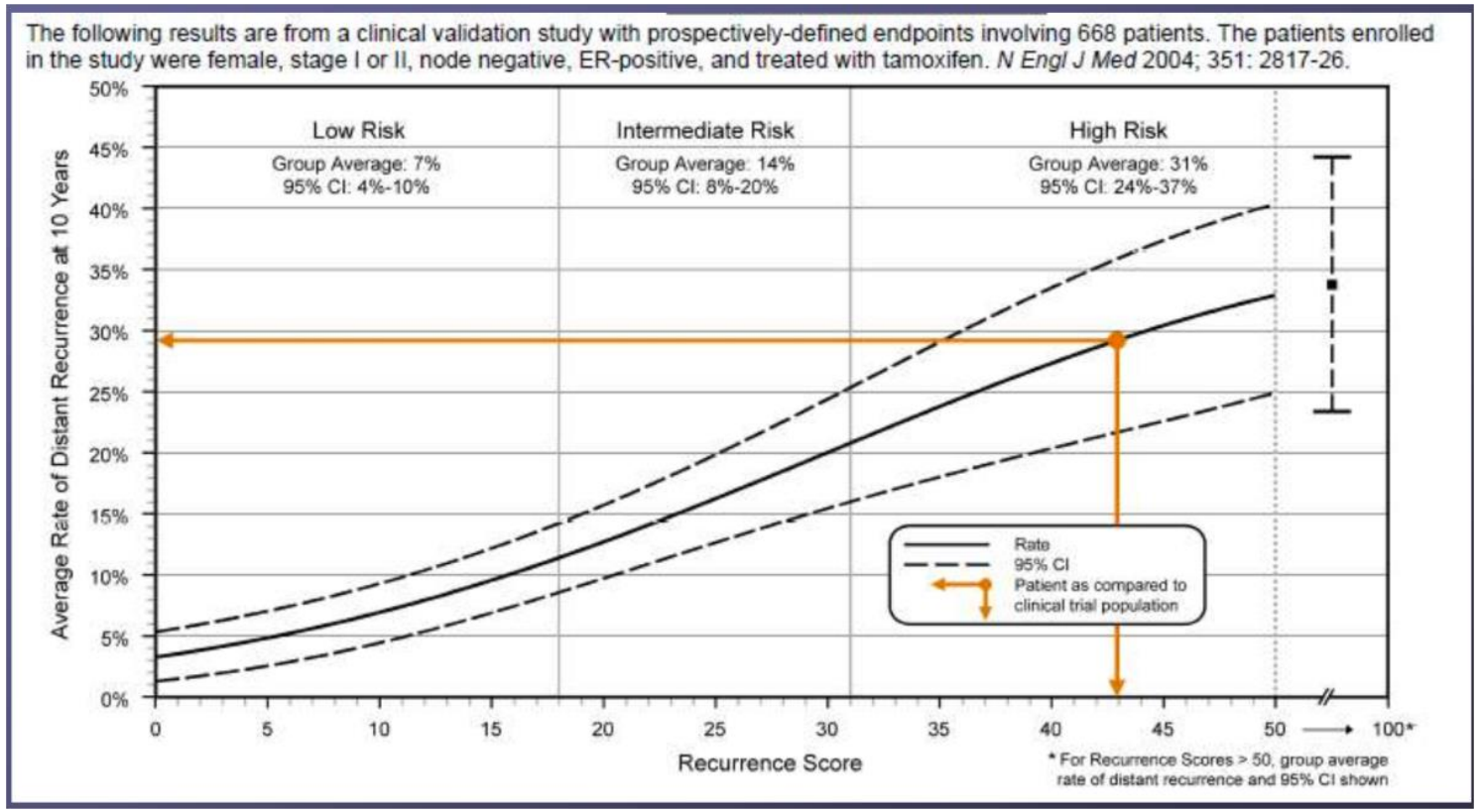

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Hormone Replacement Therapy

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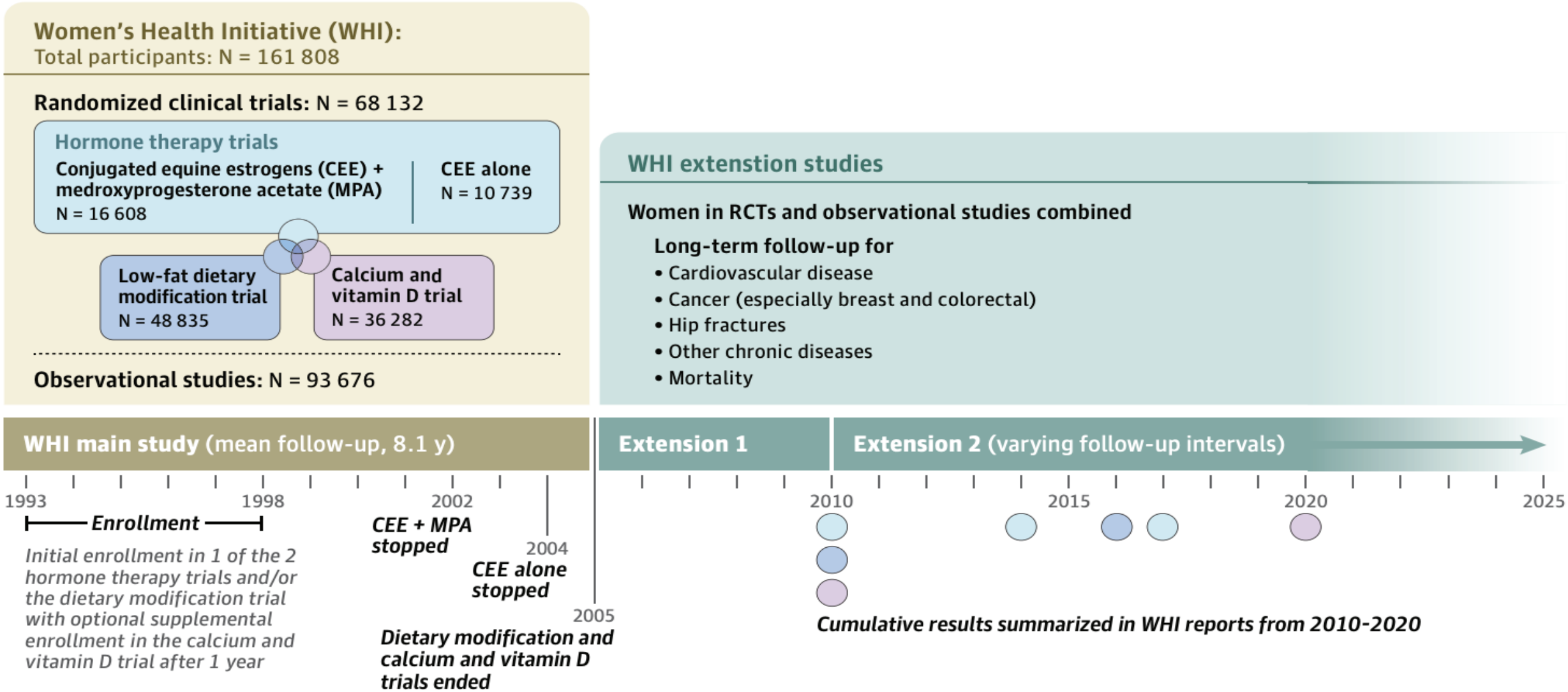
Women's Health Initiative (WHI)

- To inform clinical practice about prevention of chronic diseases (cardiovascular disease (CVD), hip fractures, breast and colorectal cancer), healthy aging, and the health effects of menopausal hormone therapy, calcium plus vitamin-D supplementation, and low-fat dietary modification.

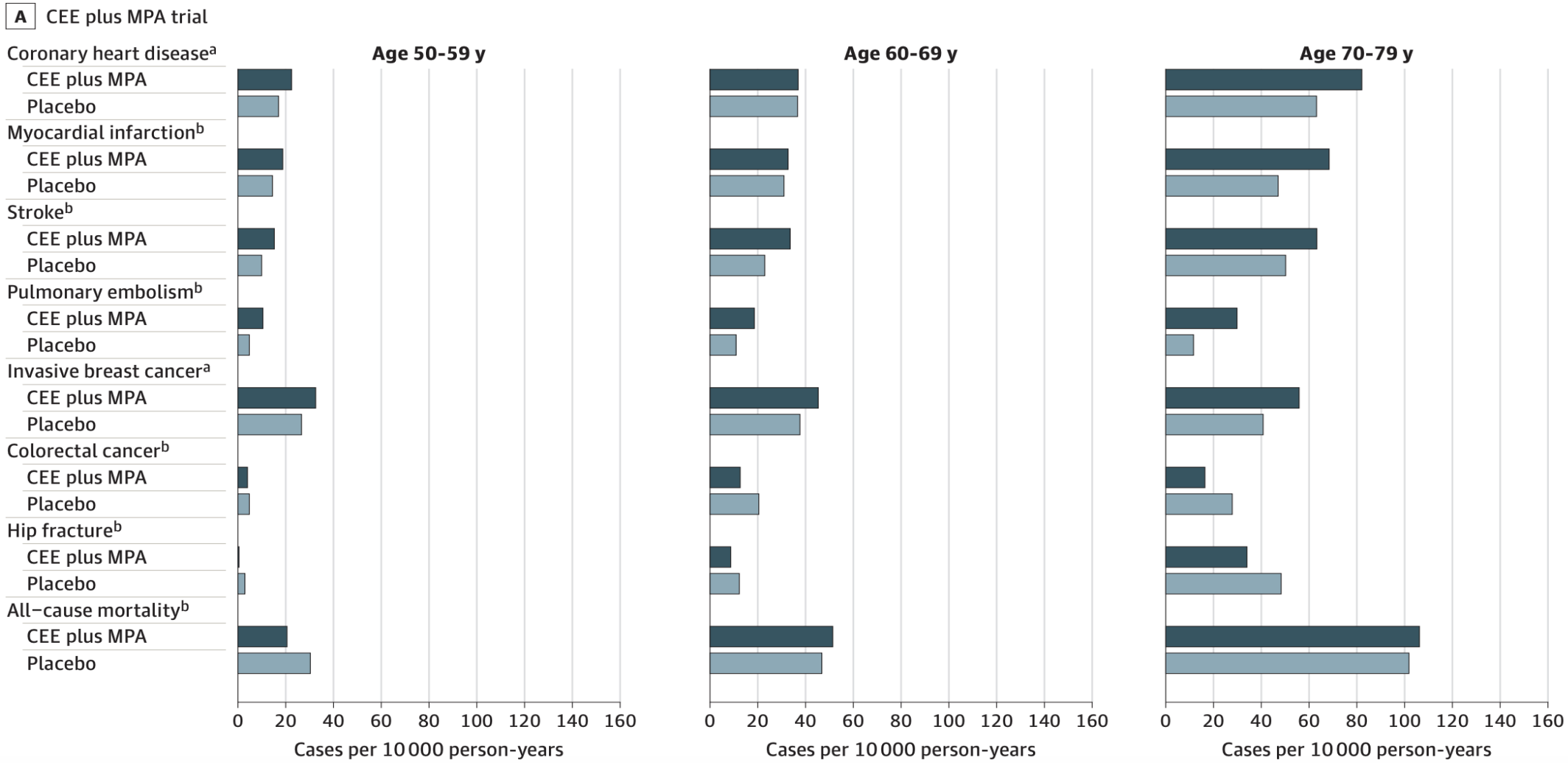
- WHI enrolled 161 808 postmenopausal US women in the clinical trials, aged 50-79 years at baseline from 1993 -1998, and followed them for 20 years.

Figure 1. Design of the Women's Health Initiative (WHI) Randomized Clinical Trials (RCTs) and Observational Study



Intervention and postintervention phases of the RCTs through Extension 1 (2010) and at varying follow-up intervals during Extension 2. Cumulative results were summarized by key WHI reports, as indicated by trial color-coded symbols on the timeline. The RCT rectangles are not drawn to scale, but the sample size of each trial is included within the relevant rectangle.

Figure 3. Absolute Risks of Health Outcomes by 10-Year Age Groups in the Women's Health Initiative Hormone Therapy Trials



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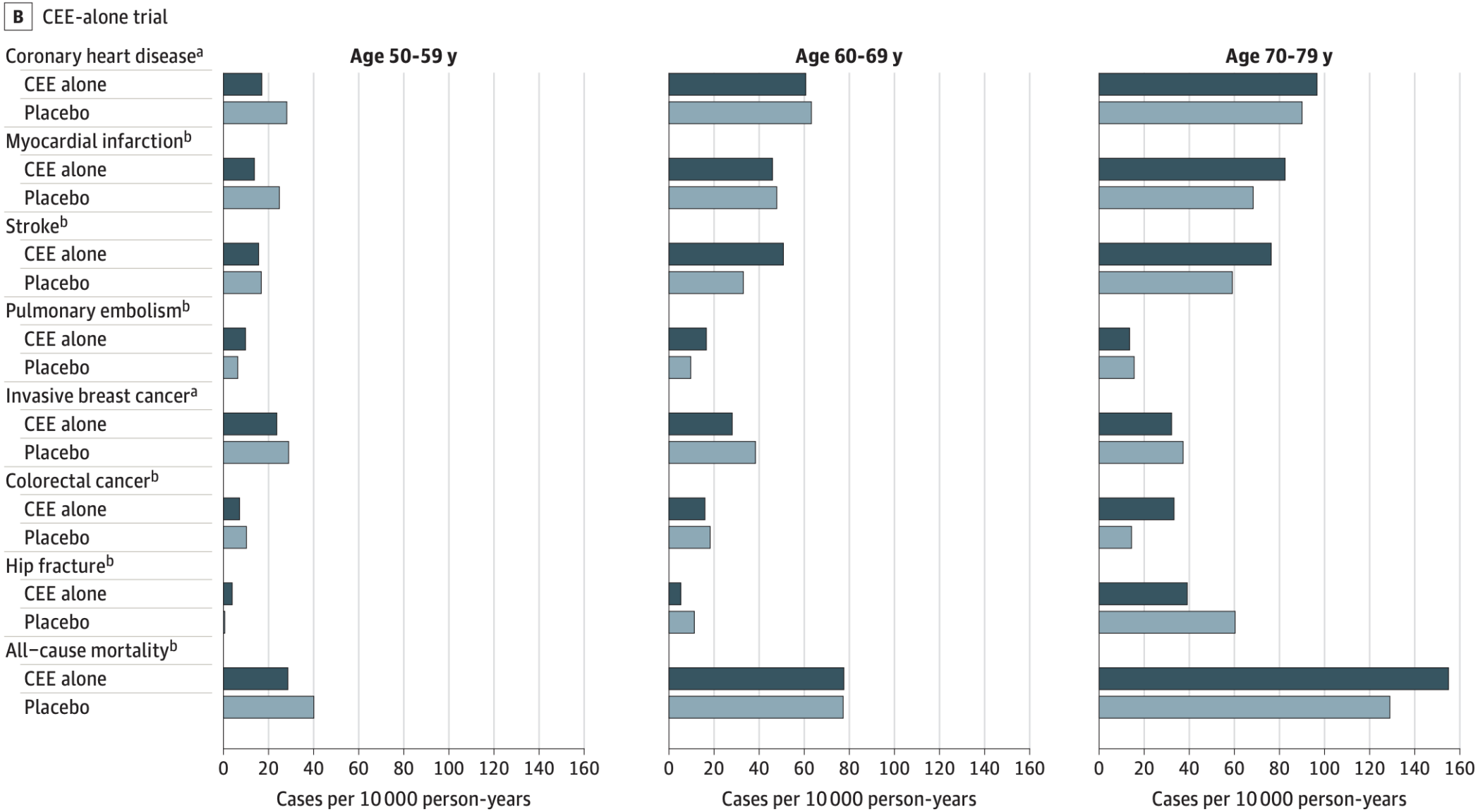

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Limitations

- "WHI hormone therapy trials tested CEE plus MPA and CEE alone, the most common hormone therapy formulations at WHI inception, but other hormone therapy formulations or routes of delivery may have yielded different results."

Table. Design, Primary Aims, and Clinical Messages of the Women's Health Initiative Randomized Clinical Trials[a]

	CEE plus MPA trial (N = 16 608)	CEE-alone trial (N = 10 739)	Calcium and vitamin D supplementation trial (N = 36 282)	Low-fat dietary modification trial (N = 48 835)
Trial-specific participant eligibility	In situ uterus; current hormone users required a 3-mo discontinuation; successful completion of 1-mo placebo run-in	Prior hysterectomy; current hormone users required a 3-mo discontinuation; successful completion of 1-mo placebo run-in	One year after randomization to hormone therapy and/or low-fat dietary modification trial, women could join the calcium and vitamin D supplementation trial.	Estimated fat intake ≥32% of energy at baseline based on a food frequency questionnaire
Interventions	Oral CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, vs placebo	Oral CEE alone, 0.625 mg/d, vs placebo	1000 mg/d of elemental calcium carbonate and 400 IU/d of vitamin D_3 vs placebo	Total fat reduction (20% of energy goal), increased vegetable and fruit intake (to ≥5 servings/d), and increased grain intake (to ≥6 servings/d) vs usual diet
Primary outcome	CHD	CHD	Hip fracture	Invasive breast cancer, colorectal cancer
Primary safety outcome	Invasive breast cancer	Invasive breast cancer		
Clinical application	Findings do not support use of CEE plus MPA to prevent CHD, stroke, dementia, or other chronic diseases, and the treatment significantly increased breast cancer risk in contrast to CEE alone. Findings in younger women support the FDA-approved indication of hormone therapy for treatment of moderate to severe vasomotor symptoms. Individualized patient care and shared decision-making are essential.	Findings do not support use of CEE alone to prevent CHD, stroke, dementia, or other chronic diseases. Findings in younger women support the FDA-approved indication of hormone therapy for treatment of moderate to severe vasomotor symptoms. Individualized patient care and shared decision-making are essential.	Calcium and vitamin D supplementation did not prevent hip fracture in postmenopausal women. Findings are consistent with the national recommended dietary allowances for intake of calcium (1200 mg/d) and vitamin D (600-800 IU/d) among postmenopausal women. Women not meeting these intake goals may benefit from supplementation.	A low-fat dietary pattern with an increase in vegetables, fruits, and grains did not significantly decrease the incidence of breast or colorectal cancer. A reduction in breast cancer mortality was observed with long-term follow-up. Such a diet provides an option for postmenopausal women seeking to reduce breast cancer risk.

Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; FDA, Food and Drug Administration; MPA, medroxyprogesterone acetate.

[a] The overall population and eligibility included 68 132 postmenopausal women (mean age, 63 years) recruited at 40 US clinical centers from 1993 to 1998. All trials required that participants be postmenopausal women aged 50 to 79 years with no prior breast cancer, with an unremarkable baseline mammogram, and with expected 3-year or longer survival. Women were excluded for major comorbid conditions or substance use disorders that could affect adherence or safety.

WHI-Conclusion

- Do not support menopausal hormone therapy to prevent cardiovascular disease or other chronic diseases.
- Menopausal hormone therapy is appropriate to treat vasomotor symptoms among women in early menopause, without contraindications.

Current Research Trends

- Personalization and De-escalation of treatment across disciplines.
- Cancer trends in young adults
- Disparities in Health Care.

Questions

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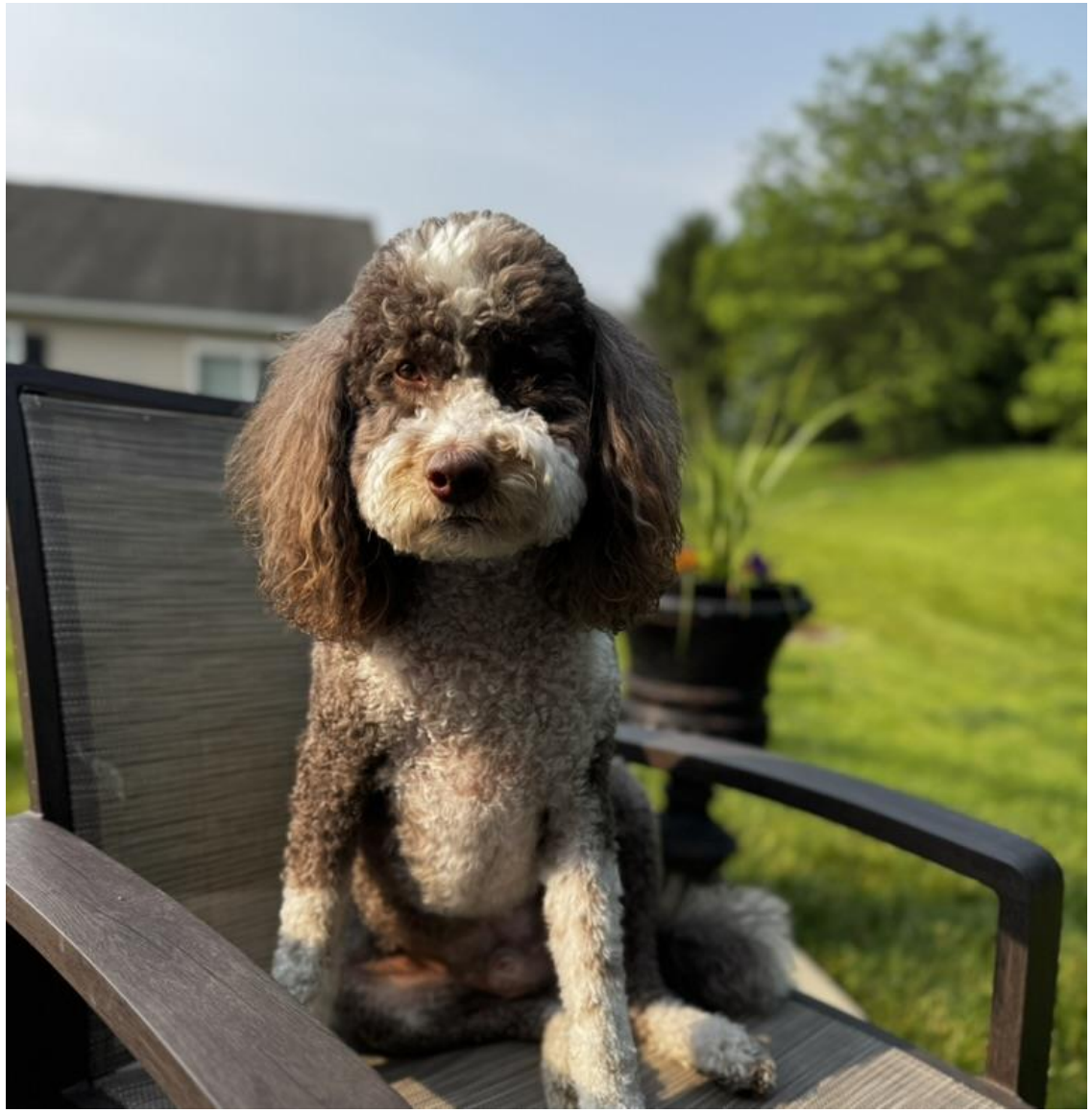

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