Estrogen Receptor-Negative and Triple Negative Breast Cancer: Epidemiological and Surgical Considerations

Ismail Jatoi, MD, PhD, FACS

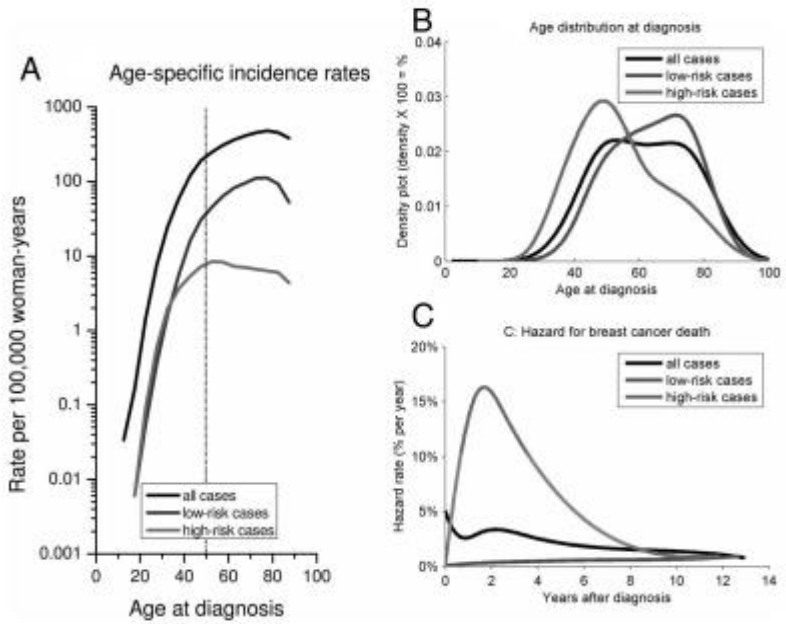
Dale H. Dorn Endowed Chair in Surgery

University of Texas Health Science Center

San Antonio, Texas USA

DEFINITION

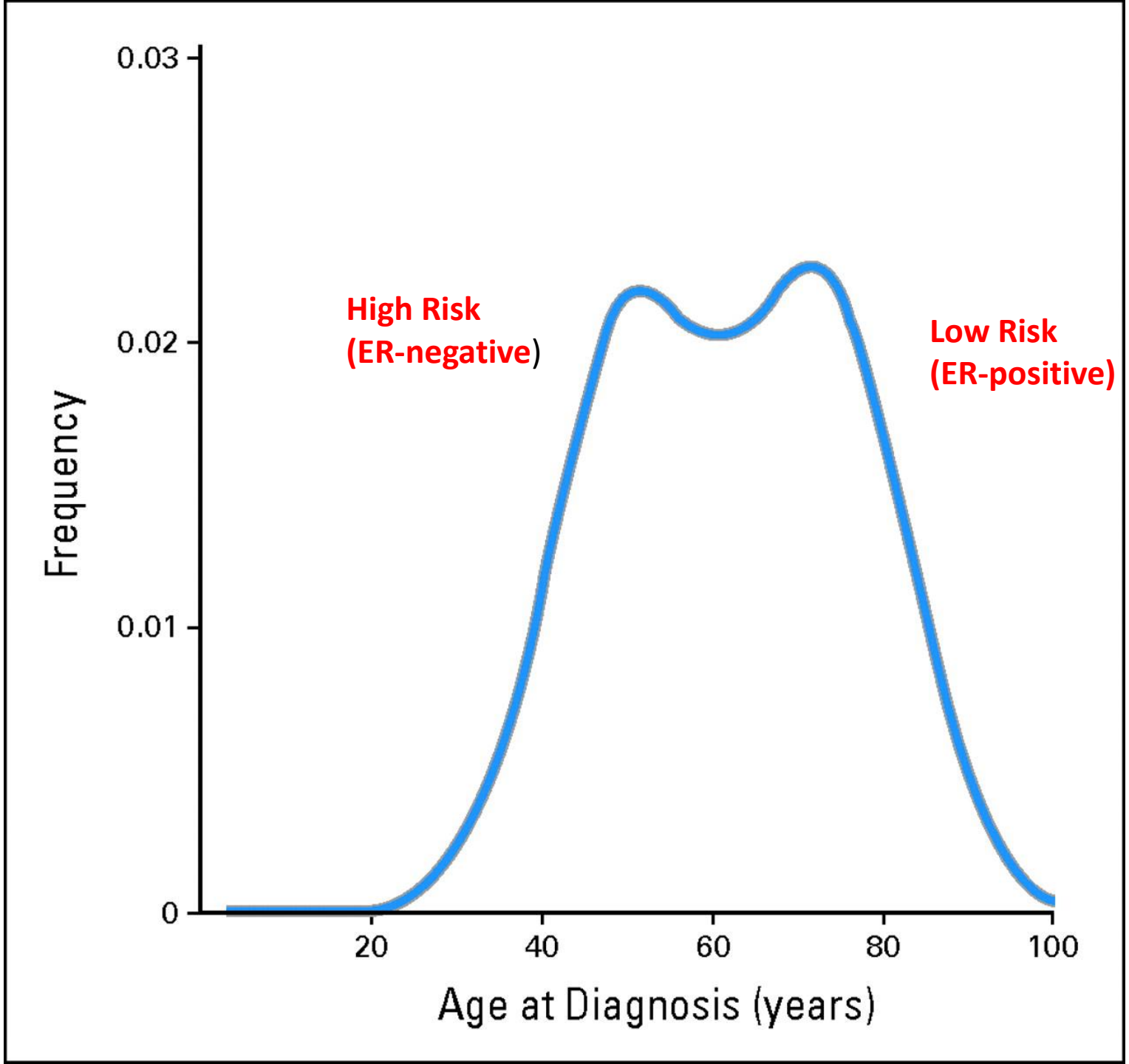
- Estrogen Receptor (ER)-negative breast cancer lacks expression of the estrogen receptor, and Triple Negative Breast Cancer (TNBC) Lacks Expression of Estrogen Receptor, Progesterone Receptor, and Human Epidermal Growth Factor Receptor (HER)- 2
- In the USA (Surveillance Epidemiology and End Results—SEER data), approximately 23% of all breast cancers are reported as Estrogen Receptor (ER)-Negative, and about 10-15% are TNBC
- Incidence of ER-positive breast is higher in parts of the world where mammography screening is widely utilized because mammography screening preferentially detects ER-positive breast cancers (Length Bias).
- High-risk (ER-negative) tumors tend to occur earlier in life (with a peak age of onset at 50 years) whereas the low-risk tumors (ER-positive) tend to occur later in life with a peak onset at 70 years.
- TNBC have a worse prognosis, and neoadjuvant systemic therapy has now become the standard of treatment, except for the small triple negative tumors



Jatoi I, et al. Am J Clin Oncol 2008; 31(5): 504-506

Age Frequency Distribution for High-Risk (ER-negative) and Low-Risk (ER-positive) breast cancers

Anderson WF, et al. JCO 2009; 32: 5308-5311



Age-Interactions in Breast Cancer Studies

- “Age-interaction” refers to differences between categories of patients according to age
- In breast cancer studies, age-interactions reflect differences between ER-negative cancers (occur more commonly in younger patients) and ER-positive cancers (occur more commonly in older patients).
- Quantitative Age-Interaction refers to instances where the size but not the direction of the effect differs according to age (i.e., a risk factor may have a greater effect on one age group when compared to another)
- Qualitative Age-Interaction refers to situations the direction of the effect is reversed according to age group (i.e., a risk factor may be associated with an increased risk in one age group but a decreased risk in another age group). Cross Over Effect. Suggest different diseases, with different natural histories, perhaps originating from different stem cells.

Examples of Qualitative Age-Interactions in Breast Cancer Studies

- Nulliparity, obesity, and use or oral J all reduce risk of early-onset breast cancer, but increase risk in older patients (Jatoi I, Anderson WF, Am J Clin Oncol 2008; 31: 504-506).
- Fenretinide (vitamin A analogue) was studied as a breast cancer prevention agent and found to reduce breast cancer risk in pre-menopausal women and increase risk in postmenopausal women. (Veronesi et al. JNCI 1999; 91: 1847-1856).
- Mammography screening trials initiated during the years 1963-1980 showed a nonsignificant increase in breast cancer mortality in women under age 50 at the start of those trials and a decrease in mortality in older women ("Mortality Paradox"). (Baines CJ, JNCI 2003; 95: 1508-1511).
- National Surgical Breast and Bowel Project (NSABP)-18 trial randomized breast cancer patients to receive Adriamycin and Cyclophosphamide (AC) either before or after surgery and found that for women younger than age 50 years, survival was better among those receiving preoperative chemotherapy, whereas for women aged over 50 years, survival was better for postoperative chemotherapy (overall there was no difference in outcome). (Wolmark N, J Natl Cancer Inst Monograph 2001; 30: 96-102).

Risk of breast cancer death after initial breast cancer diagnosis according to ER status

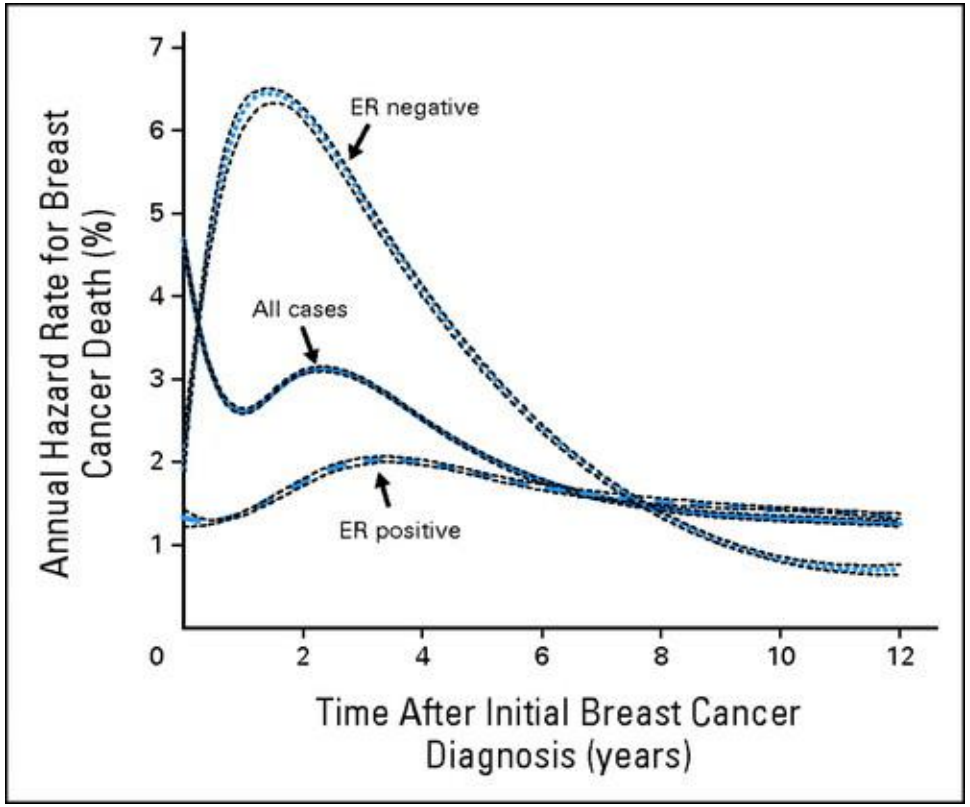


Fig 1. Annual hazard rates for breast cancer death and ER-negative to ER-positive hazard ratios (Table 1) using the National Cancer Institute's Surveillance, Epidemiology, and End Results 13 Registries Databases (1992 to 2007) for invasive female breast cancer.2 Annual hazard rates for breast cancer death overall (all cases combined, n = 401,693), estrogen receptor (ER) –negative (n = 74,567), and ER-positive (n = 257,426) breast cancers. The annual hazard rate for cancer-specific death describes the instantaneous rate of dying from cancer in a specified time interval after initial cancer diagnosis. Hazard rate curves were modeled using cubic splines with join-points selected by Akaike's information criteria3,4; 95% CIs were applied with bootstrap resampling techniques.5 Under the null hypothesis of no interaction over time, annual hazard rates for ER-positive and ER-negative breast cancers would be proportional (or similar) with follow-up after initial breast cancer diagnosis. The overall rate of breast cancer death for all cases peaks near 3% per year between the second and third years after initial breast cancer diagnosis and then declines to 1% to 2% per year by the sixth through eighth years. The annual hazard rates for women with ER-negative and ER-positive tumors demonstrate peaks of approximately 6.5% and 2% near the first through third years after initial breast cancer diagnosis, respectively (> three-fold difference). An ER-negative to ER-positive hazard rate cross-over occurs between the seventh and eighth years after breast cancer diagnosis, and then women with ER-negative tumors had a somewhat paradoxically lower rate of breast cancer death than those with ER-positive breast cancers.

Published in: Ismail Jatoi; William F. Anderson; Jong-Hyeon Jeong; Carol K. Redmond JCO 2011 05-9
DOI: 10.1200/JCO.2010.32.3550

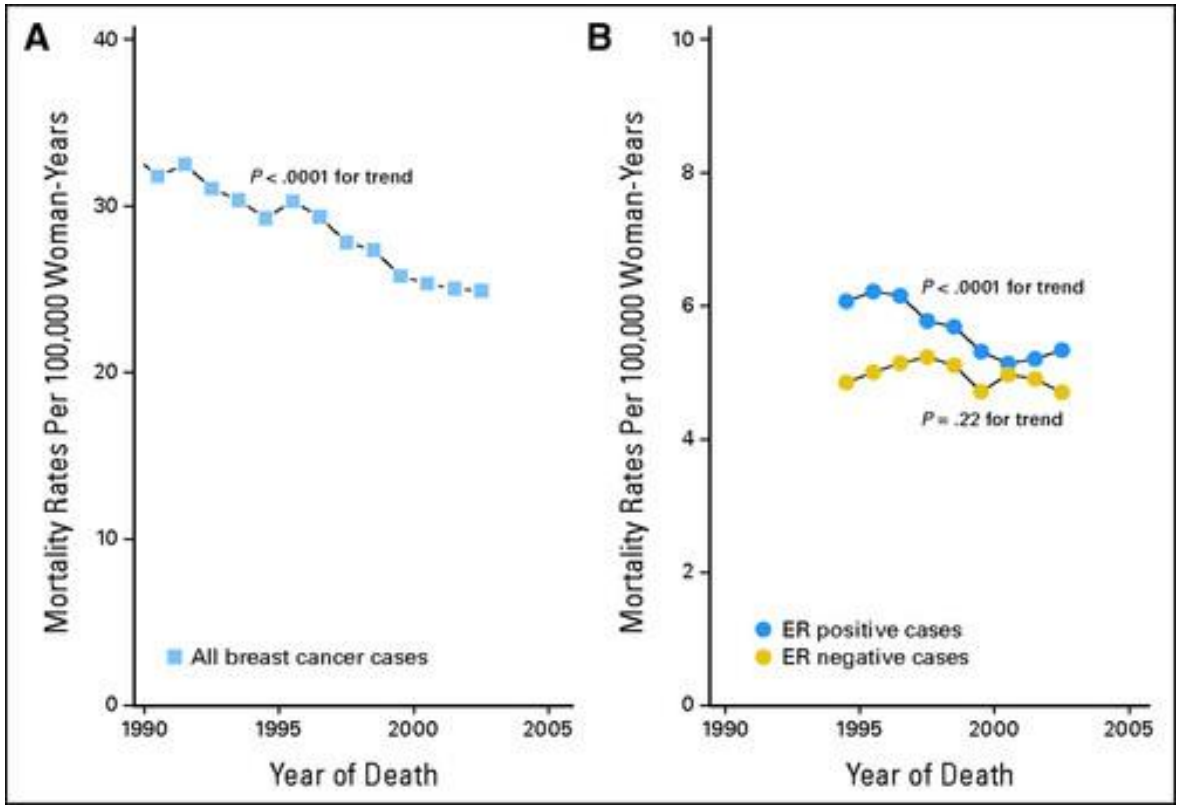


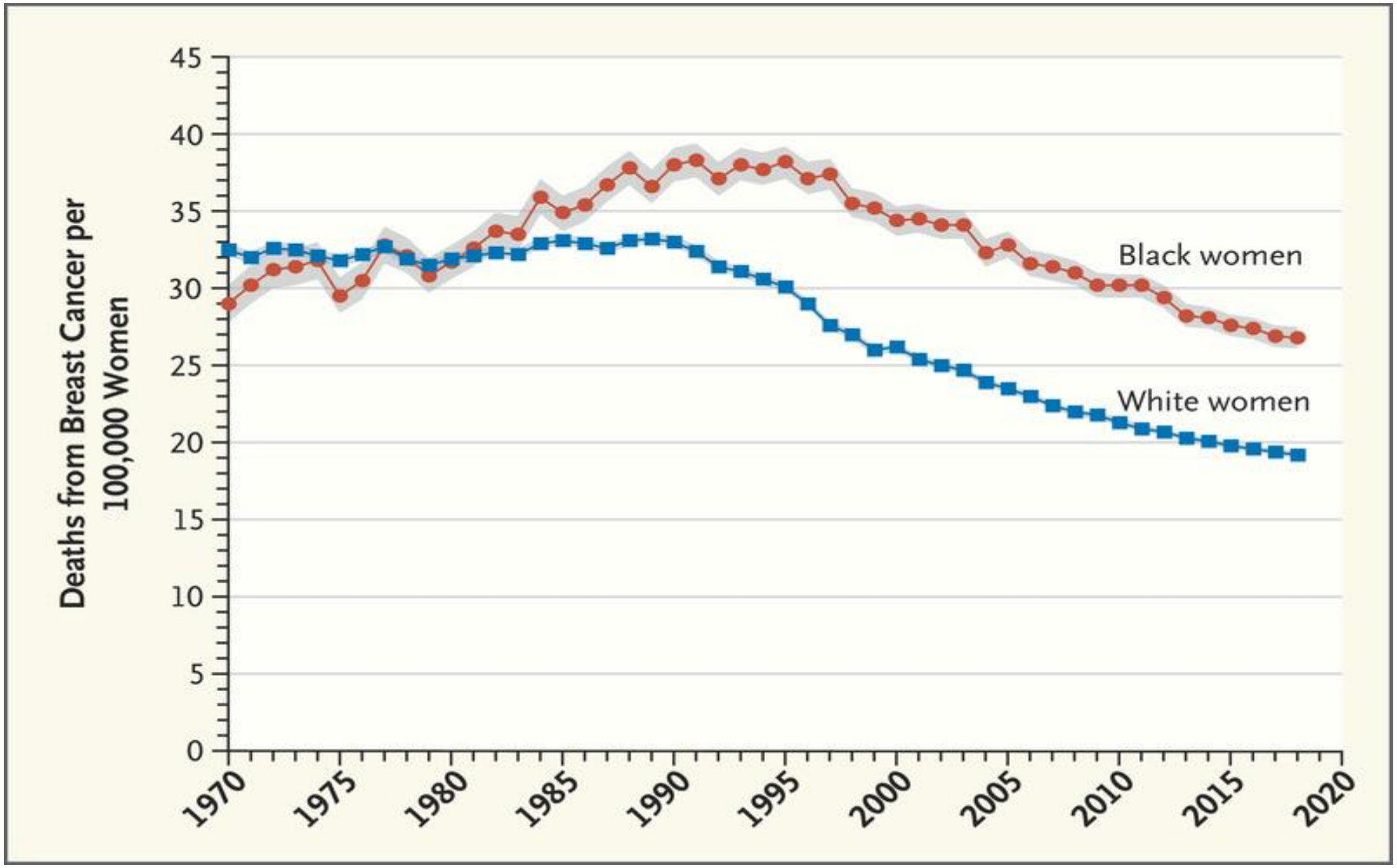
Fig 1. Age-adjusted (2000 United States standard population) breast cancer mortality rates among women with invasive breast cancer in the Surveillance, Epidemiology, and End Results 9 Registry Database for the study period 1990 to 2003. (A) Breast cancer mortality for all breast cancer cases combined. (B) Incidence-based breast cancer mortality according to estrogen receptor (ER) -positive and ER-negative expression.

Published in: Philip S. Rosenberg; William F. Anderson; Bingshu E. Chen; Ismail Jatoi JCO 2016 09-21
DOI: 10.1200/JCO.2006.09.2106

In the United States, age-adjusted breast-cancer mortality is about **40% higher among Black women than among non-Hispanic White women** (27.7 vs. 20.0 deaths per 100,000 women from 2014 through 2018), despite a lower incidence among Black women (125.8 vs. 139.2 cases per 100,000 women)

This racial disparity emerged in the 1980s

Jatoi I, et al. NEJM 2022; 386(25);2349-2352



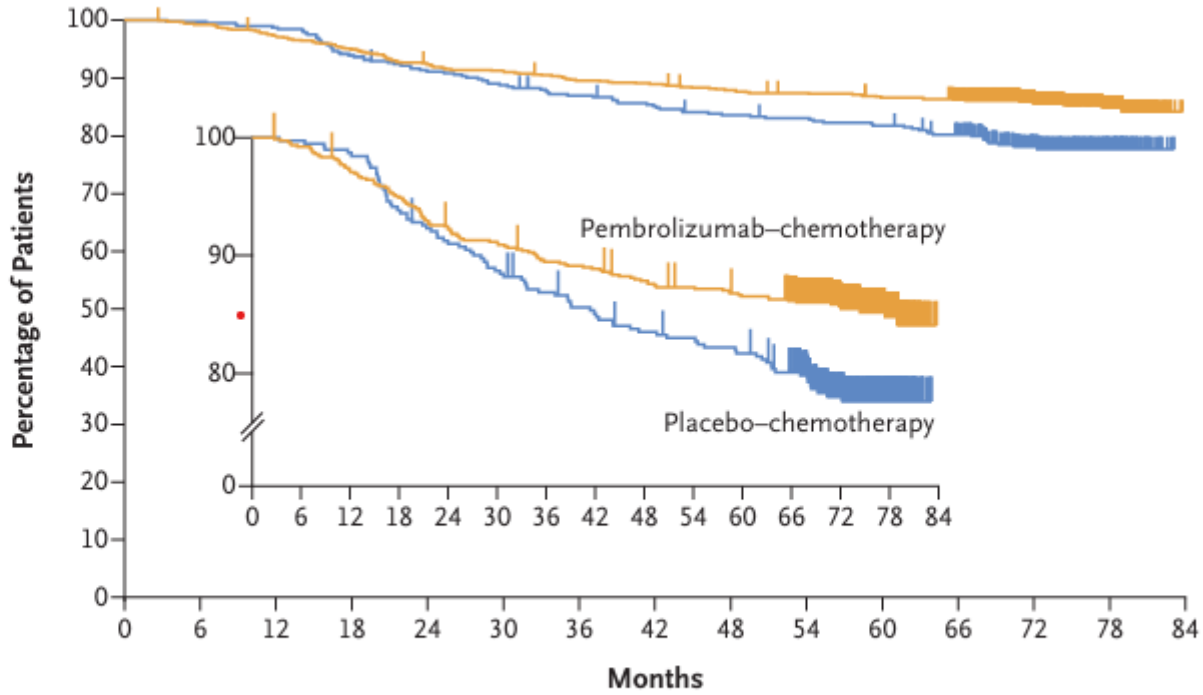
Jatoi I, et al. NEJM 2022; 386 (25); 2349-2352

Trends in Breast-Cancer Mortality among Black Women and White Women in the United States, 1970 through 2018.

What Triggered the US Racial Disparity in Breast Cancer Mortality in the 1980s?

- The introduction of novel medical interventions in the 1980s (tamoxifen and mammography screening) likely triggered this disparity.
- Both Tamoxifen and Mammography Screening primarily benefit patients with ER-positive breast cancers, and Black women have higher rates of ER-negative breast cancers (65% higher rate of any ER-negative breast cancer and 81% higher rate of triple-negative breast cancer)
- Black women often had less access to these interventions because they often lacked health insurance or had inadequate health insurance coverage.

A Overall Survival According to Treatment Group in the Intention-to-Treat Population

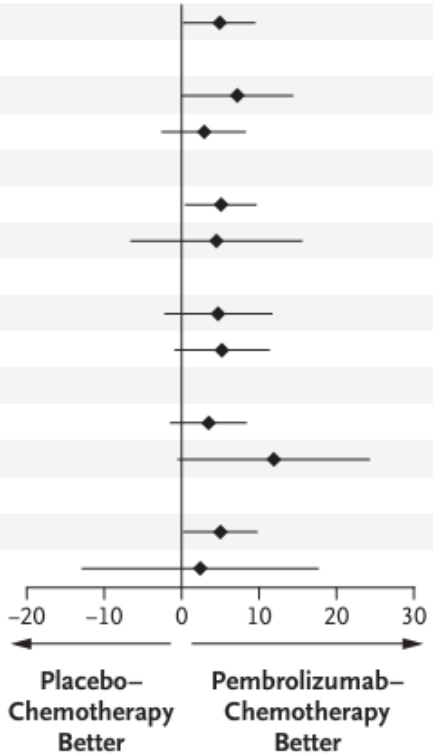


No. at Risk															
Pembrolizumab–chemotherapy	784	777	760	742	720	712	698	693	683	677	670	656	448	176	0
Placebo–chemotherapy	390	389	385	366	354	345	336	328	321	318	313	300	199	82	0

Schmid P, et al. NEJM 2024; 391: 1981-1991.

B Subgroup Analyses of Overall Survival

Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Difference in 5-Year Overall Survival (95% CI)
	no. of patients who died/total no. (%)		*percentage points*
Overall	115/784 (14.7)	85/390 (21.8)	4.9 (0.3 to 9.4)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	7.2 (0.0 to 14.3)
Negative	37/376 (9.8)	29/194 (14.9)	2.9 (–2.5 to 8.2)
Tumor size			
T1 to T2	54/580 (9.3)	51/290 (17.6)	5.1 (0.5 to 9.6)
T3 to T4	61/204 (29.9)	34/100 (34.0)	4.5 (–6.5 to 15.5)
Carboplatin schedule			
Every 3 wk	46/334 (13.8)	36/167 (21.6)	4.7 (–2.1 to 11.6)
Weekly	68/444 (15.3)	49/220 (22.3)	5.2 (–0.8 to 11.3)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	3.5 (–1.4 to 8.3)
CPS <1	23/128 (18.0)	23/69 (33.3)	11.9 (–0.4 to 24.2)
Age			
<65 yr	93/700 (13.3)	72/342 (21.1)	5.0 (0.3 to 9.7)
≥65 yr	22/84 (26.2)	13/48 (27.1)	2.4 (–12.8 to 17.6)



Schmid P, et al. NEJM 2024; 391: 1981-1991.

Summary

- Younger women have higher rates of high-risk (ER-negative) breast cancers and older women have higher rates of low-risk (ER-positive breast cancers).
- There are numerous examples of qualitative age interactions in breast cancer studies, suggesting that ER-negative and ER-positive breast cancers should perhaps be viewed as different diseases, derived from different pathways, and perhaps even originate from different stem cells
- Population-based mortality trends suggest that we have made greater progress in treating ER+positive breast cancers, and less progress in treating ER-negative breast cancers
- Neoadjuvant systemic therapy has now become the standard treatment for most patients with TNBC, and the Keynote 522 trials demonstrates a mortality benefit when chemotherapy +pembrolizumab is initiated prior to surgery.