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Trends in 5-year survival rates among breast cancer patients by hormone receptor status and stage

Lu Chen, MPH,

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington

Department of Epidemiology, University of Washington, Seattle, WA

Hannah M. Linden, MD, FACP,

Clinical Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

School of Medicine, University of Washington, Seattle

Benjamin O. Anderson, MD, and

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington

School of Medicine, University of Washington, Seattle

Christopher I. Li, MD, PhD

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington

Department of Epidemiology, University of Washington, Seattle, WA

Abstract

Purpose—Improvement in breast cancer survival has been observed in recent decades in the U.S., but it is unclear if similar survival gains are consistent across breast cancer subtypes, especially with regards to more advanced stages of the disease.

Methods—Data were from 13 population-based cancer registries participating in the Surveillance, Epidemiology and End Results (SEER) program, consisting of women between 20–79 years of age diagnosed with invasive breast cancer between 1992 and 2008. 2-year (1992–2008) and 5-year (1992–2006) breast cancer cause-specific survival rates were calculated and stratified by estrogen receptor (ER)/progesterone receptor (PR) status, stage and race. Annual percent changes in survival rates were assessed.

Results—From 1992 through 1998–1999, 5-year and 2-year cause specific survival rates significantly improved across ER+/PR+, ER–/PR– and ER+/PR– subtypes, with an annual increase ranging from 0.5%–1.0%. From 1998–1999 to 2006, different patterns were observed by

Corresponding author: Lu Chen, MPH, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, Mail Stop M4-C308, Seattle, WA 98109 (Tel: 206-667-5028; Fax: 206- 667-5948; luchen78@uw.edu).

Conflict of interest

The authors declare that they have no conflict of interest.

ER/PR subtypes with survival rates slightly improving for ER+/PR+, continuing to improve at a rate of 0.5% per year for ER-/PR-, and dropping 0.3% annually for ER+/PR-. No significant survival gains were experienced by patients with ER-/PR+ cancer during the study period. In terms of advanced diseases, greatest annual increases in survival rates were seen for patients with stage III-IV ER+/PR+ and ER-/PR- tumors but less progress was observed for advanced ER+/PR- breast cancers.

Conclusion—Steady improvements in survival rates for breast cancer have been achieved over the past several decades. However, 5-year survival rates for stage IV disease remained dismally below 20% for most ER/PR subtypes.

Keywords

breast cancer; survival; estrogen receptor; progesterone receptor; time trend

Introduction

Improvements in breast cancer survival rates have been observed in recent decades. While mortality rates increased 0.4% per year between 1975 and 1990, they have since steadily declined 1.8–3.2% annually [1]. Five-year relative survival rates have improved from 74.6% among women diagnosed between 1975 and 1979 to 90.6% for those diagnosed in 2006 [2]. Widespread mammographic screening and improved systemic treatment, primarily adjuvant endocrine therapy, are believed to be the primary contributors to the observed reduction in breast cancer mortality rates over this period [3]. However, there is some evidence that survival improvements differ by breast cancer subtypes defined by hormone receptor status, with the greatest improvements observed for estrogen receptor positive cancers [4–8].

Tumors defined by joint estrogen receptor (ER) and progesterone receptor (PR) expression have distinct phenotypic and molecular characteristics with variations in natural history and sensitivity to adjuvant hormonal therapies observed across tumor subtypes [9, 10]. Few studies have evaluated time trends in stage specific breast cancer survival rates according to joint ER/PR status. Considering these parameters together has the potential to further elucidate areas where progress has been made and where further work is needed, as screening increases the identification of early stage breast cancer [11] and endocrine therapy only provides benefit to those with hormone receptor positive disease [12, 13]. Using data from 13 population-based cancer registries participating in the Surveillance, Epidemiology and End Results (SEER) program encompassing approximately 14% of the United States population, we evaluated trends in 2-year and 5-year breast cancer specific survival rates by stage, hormone receptor status, and race.

Materials and methods

This study used data from the National Cancer Institute's SEER Program, which has routinely collected incidence and survival data from population-based cancer registries across the United States since the 1970s. Included in this study are the 13 registries that have participated in the SEER Program since 1992. These registries cover the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah; the greater metropolitan areas of

Atlanta, Detroit, Los Angeles, San Francisco-Oakland, San Jose-Monterey, and Seattle-Puget Sound; Alaska Natives; and an area of rural Georgia.

We identified a total of 376,719 women between 20 and 79 years of age who were diagnosed with invasive breast cancer and lived in the areas covered by these registries between 1992 and 2008. Women were excluded from the analysis if they had an unknown cancer stage (n=29,736) or an unknown/borderline ER/PR status (n=53,043), if they were not primary cases (n=41,456), if their cause of death was unknown (n=1,306), if they were alive without survival time (n=26) or dead due to other causes with no survival time (n=5). Therefore, the final analytic sample for 2-year survival rates consisted of 251,147 women including 162,242 ER+/PR+ patients, 53,004 ER-/PR- patients, 30,003 ER+/PR- patients, 5,898 ER-/PR+ patients. Five-year survival rates for women diagnosed with breast cancer more recently than 2006 are not yet available, therefore analysis on 5-year survival rates were based on data from 1992–2006, consisting of 137,689 ER+/PR+ cases, 45,851 ER-/PR- cases, 25,684 ER+/PR- cases, and 5,499 ER-/PR+ cases.

All study data were obtained from the publicly available SEER database using the SEER*Stat 8.1.5 statistical software (National Cancer Institute, Bethesda, MD). These include demographic and clinical characteristics such as age at diagnosis (grouped into less than 50 years of age, 50–64, and 65–79), race (white, black and others), hormone receptor status (ER+/PR+, ER-/PR-, ER+/PR- and ER-/PR+), and NCI's adjusted American Joint Committee on Cancer Classification (AJCC) stage (6th edition) (I, II, III, and IV) [14]. Our primary outcome was breast cancer cause-specific survival, which describes the probability of surviving breast cancer in the absence of other causes of death. It was derived using SEER data on vital status, cause of death, and follow-up time from breast cancer diagnosis to death or dates of last follow-up whichever came first. Demographic information and cancer related data were abstracted from medical records by trained coders at each SEER registry. Vital status of patients was both actively and passively followed up by SEER through a variety of data sources (e.g., Social Security Administration, state vital records departments, the National Death Index). Using SEER*Stat, 2-year and 5-year cause-specific survival rates were calculated for breast cancer overall and by ER/PR status. For each ER/PR subtype (ER-/PR+ was not stratified by stage due to rarity of the disease), survival trends were further assessed according to stage and race. Women of other races were not included in the race-specific analysis due to small sample size. The National Cancer Institute's Jointpoint Regression Program (Version 4.0.1) was used to calculate annual percent change in survival rates and to evaluate the statistical significance of observed time trends using a Monte Carlo permutation method [15, 16].

Results

Compared to ER+/PR+ patients, the ER-/PR- and ER-/PR+ patients were somewhat more likely to be younger, non-white, and to present with stage II-IV diseases, and the ER+/PR- patients were somewhat more likely to be older, black and to present with stage III-IV cancers (Table 1). While the numbers of cases increased over time for ER+/PR+, ER-/PR- and ER+/PR- cancers, they decreased steadily for the ER-/PR+ subtype.

From 1992 through 1998–1999, 5-year (Fig 1a) and 2-year (Fig 1b) cause specific survival rates significantly improved for patients with ER+/PR+, ER-/PR- and ER+/PR- breast cancers, with an annual increase ranging from 0.5% to 1.0%. From 1998–1999 to 2006, different patterns were observed across the ER/PR subtypes as 5-year survival rates slightly improved for ER+/PR+ disease, continued to improve at a rate of 0.5% per year for ER-/PR- disease, and dropped 0.3% annually for ER+/PR- disease. No significant survival gains were experienced by patients with ER-/PR+ cancer from 1992–2006. In absolute terms, the 5-year survival for ER-/PR- tumors remained considerably poorer compared to other types of breast cancer across all years.

Both white and black women experienced improvements in 5-year survival rates for ER+/PR+, ER+/PR-, and ER-/PR- subtypes from 1992–2006, but rates were consistently lower among black women (Fig 2). On an absolute scale these disparities narrowed somewhat for ER+/PR+ and ER+/PR- subtypes, as 5-year survival rates plateaued in recent years for whites but continued to improve for blacks, but the gap held constant for ER-/PR- breast cancer and widened somewhat for ER-/PR+ disease.

Notable differences in stage-specific survival trends were observed by hormone receptor status (Fig 3). Patients with ER+/PR+ breast cancer experienced significant survival gains across all stages, and the greatest annual increases in survival rates occurred for women diagnosed with stage III and IV disease (rising 1.0% and 2.3% per year, respectively). Similarly, improvements were consistently seen across all stages for ER-/PR- disease with rates rising 3.8% per year from 2000–2006 for stage III and 3.6% per year for stage IV ER-/PR- cancers from 1992–2006. However, in absolute terms the 5-year survival rates for stage IV ER+/PR+ and ER-/PR- were still only 38.0% and 17.4%, respectively, among cases diagnosed in 2006. Among ER+/PR- patients, survival rates for stage I cancer held essentially constant, improved at a rate of 1.0% per year for stage II cancer only from 1992–1999, steadily increased 1.5% per year for stage III cancer from 1992–2006, and increased 8.0% per year for stage IV cancer from 1992–2000 after which they declined a non-statistically significant 7.3% per year through 2006. Further examination on trends of stage IV disease across ER/PR subtypes using 2-year breast cancer specific survival rates revealed similar patterns with stage IV ER+/PR+ and ER-/PR- patients experienced rapid survival improvements (rates rising 1.2% and 3.0% respectively, data not shown) from 1992–2008 while rates of stage IV ER+/PR- had a non-statistically significant increase at 1.0% per year (data not shown). In absolute terms, 2-year survival rates were 70.2% for patients diagnosed with stage IV ER+/PR+ cancer in 2008, compared to 44.8% and 56.4% for those diagnosed with stage IV ER-/PR- and ER+/PR- diseases in 2008, respectively.

Focusing on 2-year breast cancer specific survival rates for stage IV breast cancers among the two most common tumor subtypes, ER+/PR+ and ER-/PR-, notable differences in trends by race were observed (Fig 4). There was an appreciable narrowing of the disparity in 2-year survival rates between blacks and white for ER+/PR+ breast cancer, but a widening of this disparity for ER-/PR- breast cancer such that by 2006 these rates were near equal for ER+/PR+ breast cancer, but for ER-/PR- disease these rates were 44.0% for whites and 39.2% for blacks, although the sample sizes for black women were relatively small (black

patients at risk at each year ranged from 16–65 for stage IV ER+/PR+ and 13–57 for ER–/PR–).

Discussion

Consistent with prior studies, we observed that both 2-year and 5-year cause-specific survival rates for breast cancer overall have improved since 1992 [1, 5, 17]. While earlier studies observed that improvements in breast cancer survival were largely limited to women with ER+ disease [7, 8, 18], our more recent data indicate that ER–/PR– patients have now also experienced rapid survival gains. What has not changed though are consistent differences in overall survival rates by subtype with ER+/PR+ patients having the highest survival rates and ER–/PR– patients have the lowest rates. These differences are likely largely driven by the less aggressive nature of hormone receptor positive tumors as well as the availability of effective adjuvant hormonal therapies that only benefit these patients [19–21].

Consistent survival improvements across all stages were observed for ER–/PR– breast cancer. However significant variations by stage were seen with rates rising most rapidly for stage III cancer starting in 2000, while they rose consistently for stage IV disease during the entire 1992–2006 study period. The more recent improvements in survival rates for advanced stage ER–/PR– breast cancer are likely due to enhanced therapeutic agents and options for women with ER–/PR– disease. Notable is the introduction of anti-HER2 agents such as trastuzumab (approved for use in 1998) which reduce mortality among patients with HER2+ breast cancer regardless of stage [22]. Unfortunately data on HER2 status and use of anti-HER2 therapy are not available from the SEER program over this time period, but approximately a third of ER–/PR– tumors are known to overexpress HER2 [23].

Similar to a prior study [7], rapid survival improvements for patients with ER+/PR– cancer were seen across all stages before 1999–2002. Our data suggest though that the survival improvements slowed across all stages except stage III in the more recent time period and that among stage IV ER+/PR– tumors survival rates have actually worsened since 2000. However this reversal was not apparent when examined using 2-year survival rates. Given the small number of cases with stage IV ER+/PR– in our data, this reversal could simply be a chance finding. Another issue is the enhanced reporting of weakly ER+ tumors as ER+ rather than ER– over time. In the past >10% ER expression was used to define ER positivity, however, this has shifted in recent years as current consensus guidelines mandate a lower threshold of >1% [24]. The tools used to detect ER and PR expression have also improved in their sensitivity and robustness (e.g., the use of rabbit monoclonal antibodies) resulting in the classification of more patients as ER positive [25–27]. Regardless, survival rates of ER+/PR– cancer remained markedly lower than those for ER+/PR+ disease from 1992 through 2006. It is well established that ER+/PR– breast cancer have more aggressive features (e.g., larger tumor sizes, more extensive axillary node involvement, more frequent HER2 positivity) likely accounting for this gap [28, 29]. Although the increased use of aromatase inhibitors has improved outcomes somewhat for ER+ tumors [30], adjuvant hormonal therapies provide greater benefit to ER+/PR+ patients than to ER+/PR– patients [9, 10].

In terms of racial disparities, as documented in numerous studies [31–34], we found that black women had consistently poorer survival rates compared to whites overall and across all ER/PR subtypes. Recent studies indicate that this disparity has either held constant [35, 36] or widened somewhat overall and for patients with advanced stage diseases [18, 37, 38]. Our study further evaluated this issue according to ER/PR subtype, and found that the gap has actually narrowed for patients with ER+ tumors while holding constant for ER–/PR– tumors. There is some evidence that use of adjuvant hormonal therapy is now similar among both black and white ER+ patients [39], which may have contributed to the narrowing of this disparity. On the other hand, the persistent racial differences in ER– breast cancer survival remains a concern and may be driven by ongoing differences in the utilization of other adjuvant breast cancer treatments including both chemotherapy and trastuzumab [40–42].

Given the ecologic design of this study, individual level data on a number of factors potentially relevant to these trends were not available including screening history, receipt of adjuvant treatment regimens (chemotherapy, endocrine therapy, and HER2-targeted therapy), and other personal and lifestyle factors such as body mass index, co-morbid conditions, and smoking history. A limitation of focusing on 5-year cause specific survival rates is lead time bias resulting from differential performance of screening mammography by hormone receptor status [43], and the possibility that 5-year follow-up may not be sufficient to assess any long-term survival differences by hormone receptor status [19]. However, these factors do not impact comparisons of time trends across or within each of the ER/PR subtypes assessed. Some of our results, specifically the race-specific trends, were based on small sample sizes and thus should be interpreted with caution. Lastly, given the demographics of the registries included in the SEER program, there are limitations in generalizing these results to the whole US population. In particular, the populations covered by the SEER program tend to have a higher proportion of ethnic minority and foreign-born persons than the general U.S. population [44].

Conclusion

Overall, our findings suggest that while overall steady improvements in 5 year survival rates for breast cancer have been achieved in the U.S. over the past several decades, there are subsets of breast cancer for which little progress in reducing mortality has been made. Despite the encouraging rapid improvements in survival rates for stage IV ER+/PR+ and ER–/PR– breast cancer in recent years, these improvements have been largely incremental as survival rates for stage IV breast cancer of all subtypes except ER+/PR+ remain below 20%. On-going efforts to reduce the incidence of or improve the outcomes for advanced stage breast cancer remain an important priority.

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November 2012 submission. The NCI and SEER program were not involved in the design and conduct of this study, in the analysis or interpretation of the data, or in the preparation and review of this article.

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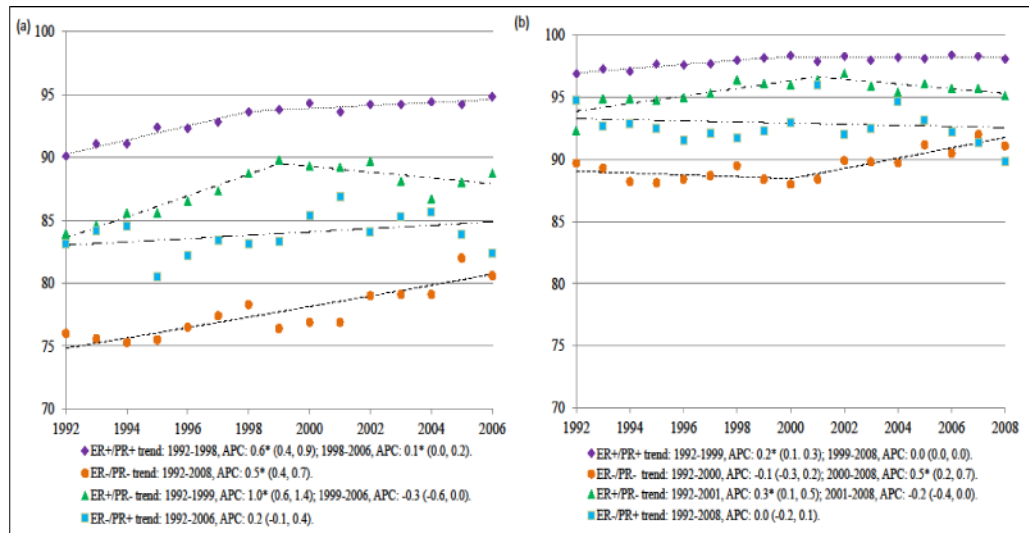
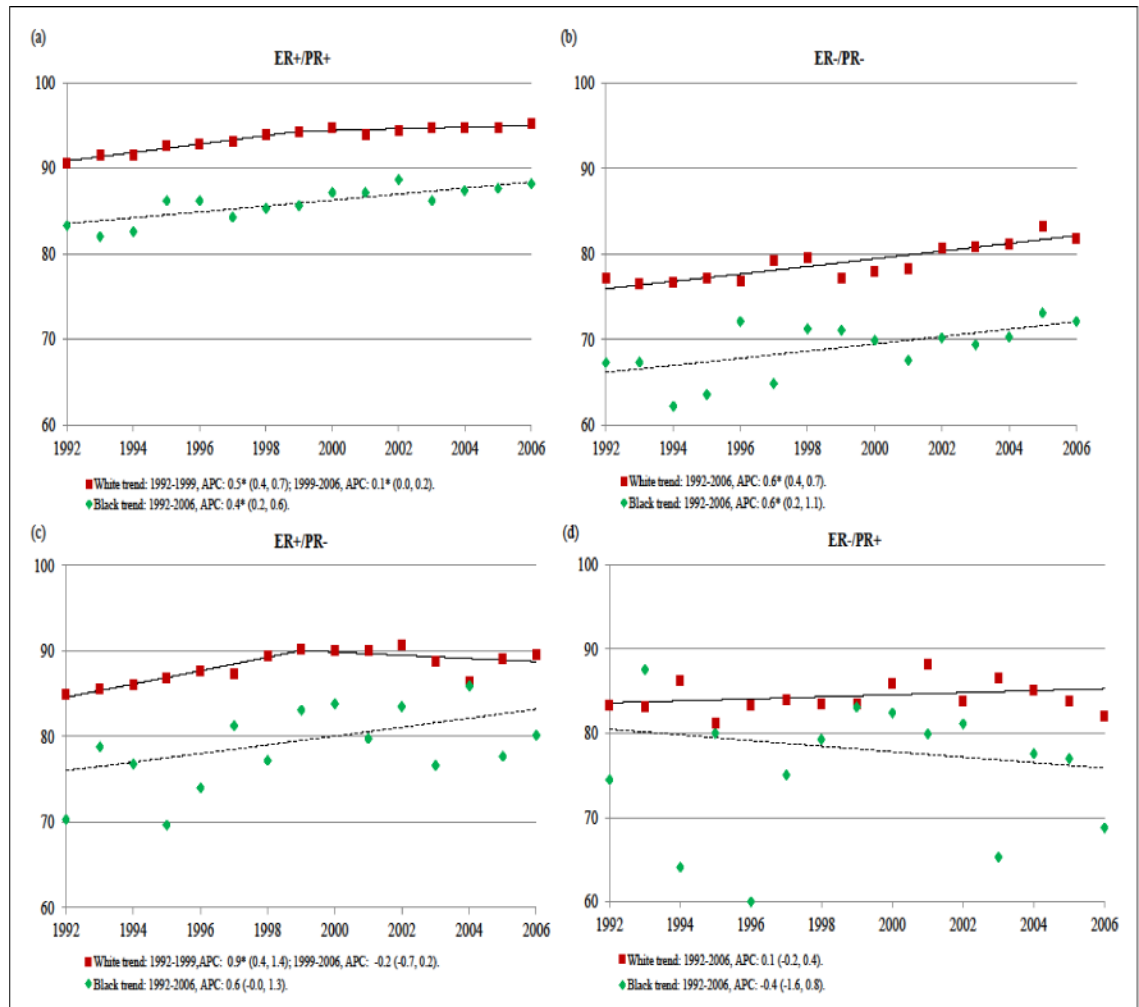


Fig 1. (a) 5-year (1992–2008), (b) 2-year (1992–2006) breast cancer specific survival rates overall and by ER/PR status



Numbers associated with the trends represent estimated annual percent change with the corresponding 95% confidence intervals in the parentheses.

* Statistically significant at 0.05.

Ranges of sample sizes (number at risk per year):

ER+/PR+: white (5,695-9,169), black (426-934).

ER-/PR-: white (1,890-2,748), black (326-647).

ER+/PR-: white (1,145-1,652), black (98-223).

ER-/PR+: white (173-414), black (17-61).

Fig 2.

Trends in 5-year breast cancer specific survival rates by race for women with (a) ER+/PR+, (b) ER-/PR-, (c) ER+/PR- and (d) ER-/PR+ diseases, 1992–2006

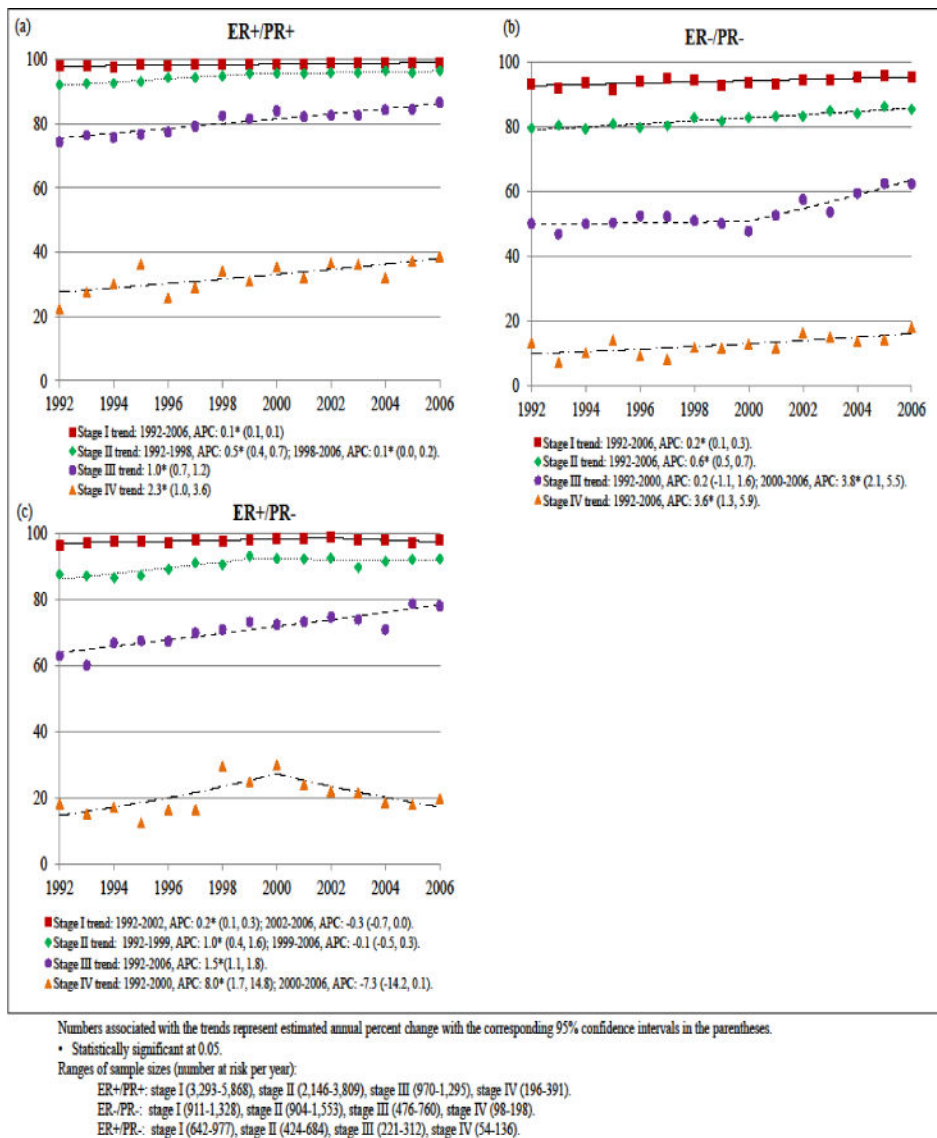
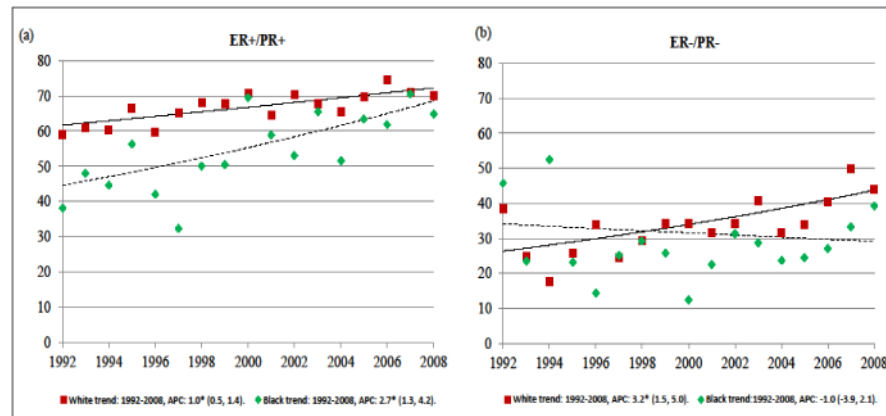


Fig 3. Trends in 5-year breast cancer specific survival rates by stage of cancer for women with (a) ER+/PR+, (b) ER-/PR-, and (c) ER+/PR- diseases, 1992–2006



Numbers associated with the trends represent estimated annual percent change with the corresponding 95% confidence intervals in the parentheses.

* Statistically significant at 0.05.

Ranges of sample sizes (number at risk per year): white ER+/PR+: 157-355; black ER+/PR+: 16-65; white ER-/PR-: 74-148; black ER-/PR-: 13-57.

Fig 4.
Trends in 2-year breast cancer specific survival rates of stage IV disease by race for women with (a) ER+/PR+ and (b) ER-/PR- cancers, 1992–2008

Table 1

Selected characteristics of breast cancer cases by hormone receptor status: 1992–2008

	ER+/PR+ (n=162,242)	ER-/PR- (n=53,004)	ER+/PR- (n=30,003)	ER-/PR+ (n=5,898)	n	Column %	n	Column %	n	Column %
Age										
<50	44,622	27.5	19,537	36.9	5,924	19.7	2,579	43.7		
50–64	63,492	39.1	21,157	39.9	12,839	42.8	2,137	36.2		
65–79	54,128	33.4	12,310	23.2	11,240	37.5	1,182	20.0		
Race										
White	134,238	82.7	39,546	74.6	24,406	81.3	4,551	77.2		
Black	10,958	6.8	8,173	15.4	2,741	9.1	675	11.4		
Other	16,434	10.1	5,107	9.6	2,750	9.2	652	11.1		
Unknown	612	0.4	178	0.3	106	0.4	20	0.3		
Stage										
I	84,191	51.9	18,781	35.4	14,061	46.9	2,437	41.3		
II	53,151	32.8	21,504	40.6	9,867	32.9	2,139	36.3		
III	19,869	12.2	10,215	19.3	4,539	15.1	1,060	18.0		
IV	5,031	3.1	2,504	4.7	1,536	5.1	262	4.4		
Year of diagnosis										
1992–1995	28,080	17.3	10,100	19.1	5,668	18.9	1,946	33.0		
1996–1999	35,926	22.1	11,746	22.2	6,555	21.8	1,675	28.4		
2000–2003	40,743	25.1	12,913	24.4	7,521	25.1	1,142	19.4		
2004–2008	57,493	35.4	18,245	34.4	10,259	34.2	1,135	19.2		
SEER registry										
San Francisco-Oakland, CA	20,889	12.9	5,996	11.3	3,830	12.8	642	10.9		
Connecticut	16,479	10.2	5,532	10.4	3,132	10.4	615	10.4		
Detroit, MI	16,002	9.9	6,528	12.3	3,458	11.5	649	11.0		
Hawaii	6,521	4.0	1,709	3.2	1,033	3.4	306	5.2		
Iowa	14,217	8.8	4,464	8.4	2,502	8.3	700	11.9		
New Mexico	6,394	3.9	2,066	3.9	1,297	4.3	255	4.3		

	ER+/PR+ (n=162,242)	ER-/PR- (n=53,004)	ER+/PR- (n=30,003)	ER-/PR+ (n=5,898)	n	Column n %	n	Column n %
Seattle, WA	22,773	14.0	6,053	11.4	3,517	11.7	463	7.9
Utah	7,127	4.4	2,236	4.2	1,075	3.6	209	3.5
Atlanta, GA	10,965	6.8	4,536	8.6	2,065	6.9	475	8.1
San Jose, CA	9,850	6.1	2,816	5.3	1,864	6.2	289	4.9
Los Angeles, CA	30,293	18.7	10,751	20.3	6,088	20.3	1,264	21.4
Alaska Natives	316	0.2	115	0.2	65	0.2	9	0.2
Rural Georgia	416	0.3	202	0.4	77	0.3	22	0.4