Breast Cancer Research and Treatment (2019) 173:743–747
https://doi.org/10.1007/s10549-018-5042-1

BRIEF REPORT

Trends in stage at diagnosis for young breast cancer patients in the United States

Carol E. DeSantis[1,2] · Jiemin Ma[1] · Ahmedin Jemal[1]

Received: 7 September 2018 / Accepted: 8 November 2018 / Published online: 13 November 2018

Abstract

Purpose Previous studies reported increasing rates of metastatic breast cancer among young US women. However, these studies were based on limited geographic areas and did not account for the sharp decline in unknown-stage disease. In this study, we examined trends in early-onset breast cancer incidence rates by stage at diagnosis in a national dataset, after correcting for temporal changes in unstaged disease.

Methods Using data from 42 states, covering 82% of the US population, we examined trends in incidence rates by stage at diagnosis and race/ethnicity in women ages 20–39 years. Stage was imputed for non-Hispanic (NH) white and NH black cases with missing information by distributing cases proportionally according to survival statistics.

Results During 2001–2015, incidence rates of early-onset metastatic breast cancer increased sharply among NH white, NH black, Hispanic, and Asian/Pacific Islander (API) women. Increasing trends were also observed for local-stage disease (all racial/ethnic groups) and regional-stage disease (NH white and API). In contrast, rates decreased sharply for unstaged disease among all groups. After imputing stage for cases with missing information, the increasing trends for regional- and distant-stage disease in NH whites and local-stage disease in NH blacks were no longer statistically significant, but the increase in distant-stage disease in NH blacks was unchanged.

Conclusions After accounting for the sharp decline in unstaged cases, the increase in incidence rates for distant-stage disease became non-significant in NH whites but not in NH blacks. Future studies should consider accounting for temporal changes in unstaged disease when examining stage-specific incidence trends.

Keywords Breast cancer · Incidence trends · Young women · Stage at diagnosis

Background

In 2013, Johnson et al. reported that the incidence rate for breast cancers diagnosed at distant-stage increased by 2.1% per year on average during 1976–2009 for women ages 25–39 [1]. A subsequent study found rates of distant-stage breast cancers increased by 6.9% per year from 1997 to 2011 in women under 40 years [2]. Both of these studies relied on data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, which covered only 9–28% of the US population. In addition, these studies did not adjust for the sharp decline in unstaged cases over the study period, although Johnson et al. conclude that the decline in unstaged disease was unlikely to explain the increase in distant-stage disease [1]. Herein, we extend these studies using a large, national population-based database to examine contemporary trends in breast cancer incidence rates from 2001 to 2015 by stage at diagnosis and race/ethnicity among women ages 20–39 in the US after correcting for declining rates of unstaged disease.

Methods

Population-based cancer incidence data in the US are collected by the SEER program and the Centers for Disease Control and Prevention's National Program of Cancer Registries and are compiled by the North American Association of Central Cancer Registries (NAACCR). Incidence data from

✉ Carol E. DeSantis
carol.desantis@cancer.org

[1] Surveillance and Health Services Research, American Cancer Society, Atlanta, GA, USA

[2] American Cancer Society, 250 Williams Street, Atlanta, GA 30303, USA

NAACCR, which included 42 states representing 82% of the US population, were used to describe trends in invasive breast cancers diagnosed in women ages 20–39 years during 2001–2015 [3]. Data from Kansas, Maryland, Minnesota, Mississippi, Nevada, New Mexico, Tennessee, Virginia, and the District of Columbia were not included because these states failed to meet NAACCR high-quality standards for 1 or more years during the study period or did not consent to participate in this study. Stage at diagnosis was defined using SEER Summary stage.

All incidence rates were age-standardized to the 2000 US standard population and expressed per 100,000 women and were calculated using the NCI's SEER*Stat software (version 8.3.4) [4]. Incidence rates were adjusted for delays in reporting to account for the additional time required for registration of some cases [5]. Delay-adjustment ratios from the SEER 18 areas for invasive breast cancer cases diagnosed at ages 20–39 were applied to the NAACCR data by racial/ethnic group, stage, and year of diagnosis [6]. Trends in breast cancer incidence rates were examined using Joinpoint software (version 4.2.0.2), with the resulting trends expressed as annual percent change (APC) [7].

In order to assess the effects of the decline in unstaged cases on the incidence trends for known stages, we partitioned unstaged cases into localized, regional, and distant groups, based on the 5-year survival in SEER-18 for each stage and year of diagnosis, and conditional on the combined survival of these "restaged" cases equaling the observed survival of the unstaged cases. That is, the combined survival for the unstaged cases was estimated as $(p^{\text{local}} * S^{\text{local}} + p^{\text{regional}} * S^{\text{regional}} + p^{\text{distant}} * S^{\text{distant}})/100$, where p represents the percentage and S represents the observed relative survival for localized, regional, and distant cases, respectively. Briefly, we first partitioned all unstaged cases into regional and localized/distant groups, depending on where the observed survival of unstaged cases lies. We then further partitioned a portion of those "restaged" regional cases into localized and distant cases assuming the same percentage of regional cases among staged and unstaged cases. We only imputed stage for non-Hispanic (NH) white and NH black cases due to small case counts for other racial/ethnic groups.

Results

There were 134,518 women ages 20–39 years diagnosed with invasive breast cancer during 2001–2015 in the 42 states included in the analysis. From 2001 to 2015, overall incidence rates increased slightly among NH white (0.5% per year), NH black (0.3% per year) and Asian/Pacific Islander (API, 1.0% per year) women but were stable among Hispanic women (Table 1). In analyses not adjusted for unknown-stage, increasing trends were observed for local-stage disease in all racial/ethnic groups and for regional-stage disease among NH white and API women (Table 1; Fig. 1). Rates of distant-stage disease also increased sharply among all racial/ethnic groups during the study period. However, a concomitant sharp decrease (3.9–5.3% per year) in unknown-stage disease occurred among all racial/ethnic groups. In stage-specific analyses adjusted for declines in unstaged cases (limited to NH whites and blacks), incidence rates were statistically significantly increasing only for local-stage disease in NH whites and distant-stage disease in NH blacks (Table 1).

Discussion

Based on a nationwide database, we found that incidence rates of early-onset *de novo* metastatic breast cancer (unadjusted for changes in unstaged disease) increased sharply in NH white, NH black, Hispanic, and API women aged 20–39 years in the US during the most recent time period, confirming and extending the previous findings based on limited geographic areas [1, 2]. For the first time, however, we show that the increase in distant-stage disease among NH white women is no longer statistically significant after 2008 when adjusted for the sharp decline in unstaged disease because of improved stage ascertainment over the study period.

Unstaged cases in cancer registry data result from insufficient information on tumor size, lymph nodes, and/or metastases in the medical record to assign stage. These cases are more common in non-whites, uninsured, or in patients residing in rural areas [8, 9], and also occur more frequently in patients residing in the South compared to other regions. During 2011–2015, 4% of breast cancer cases were unstaged in patients residing in Southern states, compared to 1–2% for women in other regions (data not shown) [3]. Factors that may have contributed to the sharp decline in unstaged cases include general improvement in the quality and completeness of cancer registry data, including the 2004 implementation of the collaborative staging system which utilizes a computer algorithm to stage cases. It is also possible that increased use of positron emission tomography scans to stage cancers among patients who did not undergo surgery or otherwise were unable to be staged, such as elderly patients or those with comorbid conditions, may have contributed to the decline in the incidence of unstaged disease [8].

In contrast to the trend in NH white women, the increasing incidence trend for distant-stage disease in NH black women was not affected by adjustment for the decline in unstaged cases. One factor may be the upstaging of more advanced regional-stage disease due to increased use of imaging [10]. However, that is unlikely to fully explain the rising incidence of distant-stage disease in blacks, as incidence rates

Table 1 Incidence rates and trends in breast cancer incidence rates by stage at diagnosis and race/ethnicity, ages 20–39

	Incidence rates per 100,000 and 95% confidence intervals		Joinpoint analyses				
			Trend 1		Trend 2		
	2001–2003	2013–2015		Years	APC	Years	APC
Non-Hispanic white							
All stages	27.1 (26.7, 27.5)	28.8 (28.4, 29.3)		2001–2015	0.5*		
Localized	13.1 (12.9, 13.4)	14.1 (13.8, 14.4)		2001–2010	0.0	2010–2015	1.8*
			Imputed trend	*2001–2010*	*−0.2*	*2010–2015*	*1.7**
Regional	11.7 (11.5, 12.0)	12.3 (12.0, 12.6)		2001–2015	0.3*		
			Imputed trend	*2001–2015*	*0.2*		
Distant	1.1 (1.1, 1.2)	1.9 (1.8, 2.0)		2001–2008	6.8*	2008–2015	1.8*
			Imputed trend	*2001–2008*	*5.4**	*2008–2015*	*0.8*
Unstaged	1.1 (1.0, 1.2)	0.6 (0.5, 0.6)		2001–2015	−5.3*		
Non-Hispanic black							
All stages	32.0 (31.0, 33.0)	33.4 (32.4, 34.4)		2001–2015	0.3*		
Localized	13.0 (12.4, 13.6)	13.7 (13.1, 14.4)		2001–2015	0.5*		
			Imputed trend	*2001–2015*	*0.2*		
Regional	14.8 (14.2, 15.5)	14.7 (14.1, 15.4)		2001–2015	−0.1		
			Imputed trend	*2001–2015*	*−0.3*		
Distant	2.4 (2.1, 2.7)	3.9 (3.5, 4.2)		2001–2015	3.7*		
			Imputed trend	*2001–2015*	*3.7**		
Unstaged	1.8 (1.6, 2.0)	1.1 (0.9, 1.2)		2001–2015	− 5.0*		
Hispanic							
All stages	21.2 (20.5, 21.9)	22.0 (21.3, 22.6)		2001–2015	0.2		
Localized	8.8 (8.3, 9.3)	9.5 (9.1, 10.0)		2001–2015	0.6*		
Regional	10.0 (9.5, 10.5)	10.1 (9.6, 10.5)		2001–2015	−0.3		
Distant	1.1 (0.9, 1.3)	1.6 (1.4, 1.8)		2001–2015	2.9*		
Unstaged	1.3 (1.1, 1.5)	0.8 (0.7, 0.9)		2001–2015	−3.9*		
Asian/Pacific Islander							
All stages	22.6 (21.4, 23.8)	25.4 (24.3, 26.5)		2001–2015	1.0*		
Localized	11.1 (10.3, 12.0)	13.1 (12.3, 13.9)		2001–2015	1.3*		
Regional	9.5 (8.7, 10.3)	10.1 (9.4, 10.8)		2001–2004	−4.9	2005–2015	1.4*
Distant	0.9 (0.7, 1.2)	1.6 (1.4, 1.9)		2001–2015	2.9*		
Unstaged	1.0 (0.8, 1.3)	0.6 (0.4, 0.8)		2001–2015	−4.6*		

All rates are age adjusted to the US standard population and adjusted for delays in case reporting. Imputed trends have been adjusted for cases with missing stage at diagnosis

Italics indicate trends adjusted for declines in unstaged disease

*Indicates trends are significantly different from 0.0, $p < 0.5$

for regional-stage disease remained unchanged during the study period; although, we cannot rule out that there was no upstaging of local-stage disease through imaging that could have offset upstaging of regional-stage diseases. Nevertheless, the increasing trend in distant-stage disease in blacks requires further investigation.

This study is the largest, population-based study of stage at diagnosis in early-onset breast cancer in the US. However, our study has several limitations. We used race/ethnicity- and stage-specific survival instead of medical chart review for redistribution of unstaged disease to known stage diseases. We also limited the redistribution of unstaged diseases to NH whites and NH blacks because of sparse data for the other racial and ethnic groups. As a result, we were unable to examine adjusted stage-specific trends in Hispanic or API women.

In conclusion, incidence rates of early-onset *de novo* metastatic breast cancer continue to increase in NH black women but have leveled off in NH white women after adjusting for the sharp decline in unstaged disease over the past decades. Future studies on stage-specific incidence trends should consider accounting for temporal changes in unstaged diseases. Also, further studies are needed to identify reasons for the increasing rates of metastatic breast cancer in young black women.

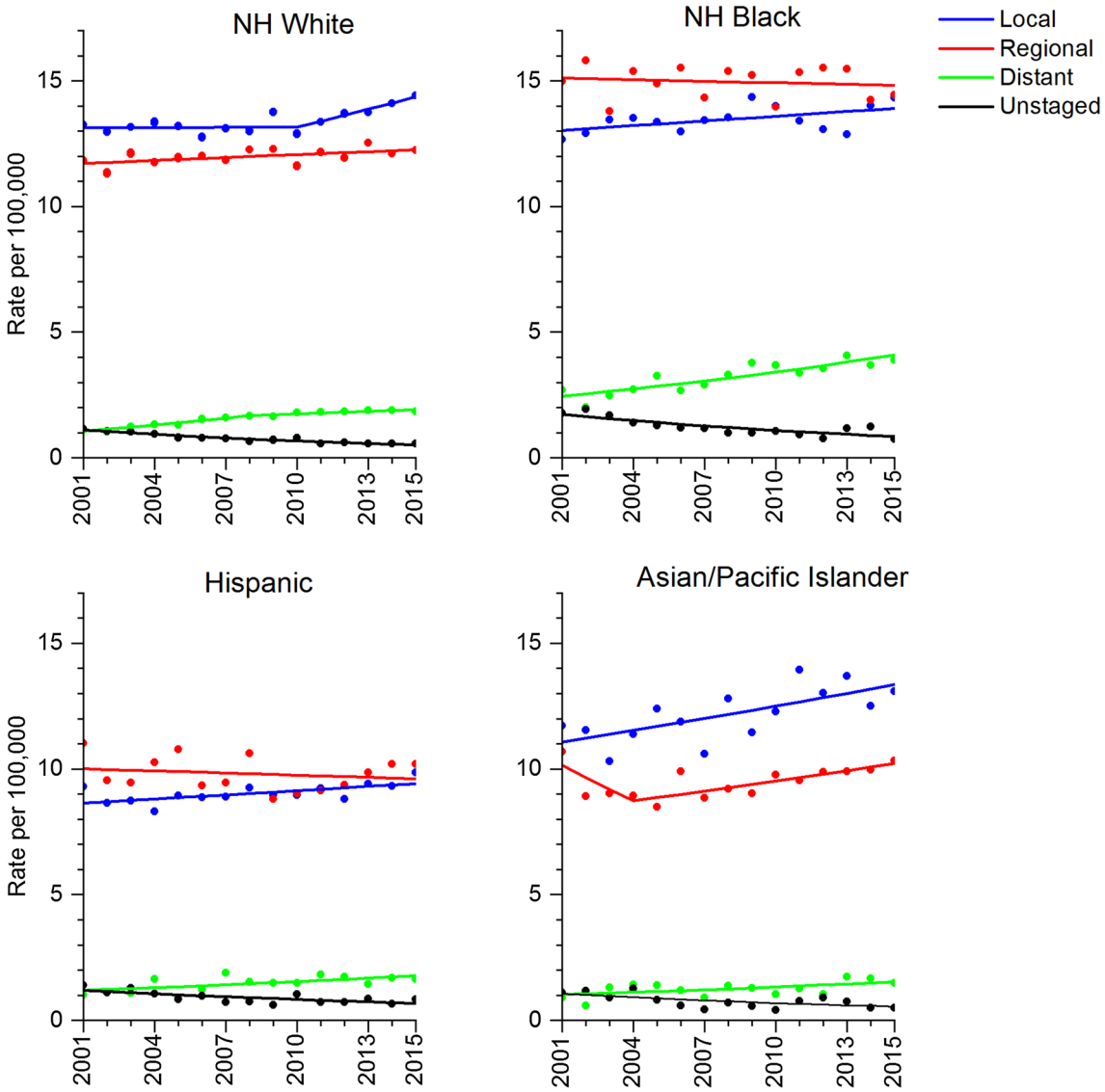

Fig. 1 Trends in breast cancer incidence rates by stage at diagnosis among US women aged 20–39. Rates are age adjusted to the US standard population and adjusted for delays in case reporting. Solid lines indicate Joinpoint fitted trends and circles represent observed data. *Source* North American Association of Central Cancer Registries, 2018

Funding No external funding applies.

Data Availability The dataset generated and analyzed during the current study is available from the North American Association of Cancer Registries, https://www.naaccr.org/cina-data-products-overview.

Compliance with ethical standards

Conflict of interest The authors are employed by the American Cancer Society, which received a Grant from Merck, Inc., for intramural research outside the submitted work; however, their salary is solely funded through American Cancer Society funds.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Johnson RH, Chien FL, Bleyer A (2013) Incidence of breast cancer with distant involvement among women in the United States, 1976 to 2009. JAMA 309(8):800–805. https://doi.org/10.1001/jama.2013.776
2. Di Meglio A, Freedman RA, Lin NU, Barry WT, Metzger-Filho O, Keating NL, King TA, Sertoli MR, Boccardo F, Winer EP, Vaz-Luis I (2016) Time trends in incidence rates and survival of newly diagnosed stage IV breast cancer by tumor histology: a population-based analysis. Breast Cancer Res Treat 157(3):587–596. https://doi.org/10.1007/s10549-016-3845-5
3. SEER*Stat Database: NAACCR Incidence Data—CiNA Analytic File, 1995–2015, Public Use, certified by the North American Association of Central Cancer Registries (NAACCR) as meeting

high-quality incidence data standards for the specified time periods (December 2016)
4. Surveillance Research Program, National Cancer Institute SEER*Stat software version 8.3.4. http://www.seer.cancer.gov/seerstat
5. Clegg LX, Feuer EJ, Midthune DN, Fay MP, Hankey BF (2002) Impact of reporting delay and reporting error on cancer incidence rates and trends. J Natl Cancer Inst 94(20):1537–1545
6. Surveillance, Epidemiology, and End Results (SEER) Program (http://www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 18 Regs Research Data + Hurricane Katrina impacted Louisiana cases, Nov 2017 Sub (1973–2015 varying)—linked to county attributes—total U.S., 1969–2013 counties. National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2018, based on the November 2017 submission
7. Joinpoint Regression Program, Version 4.5.0.2. June, 2018. Statistical Research and Applications Branch, National Cancer Institute
8. Herget K, Stroup A, Smith K, Wen M, Sweeney C (2017) Unstaged cancer: long-term decline in incidence by site and by demographic and socioeconomic characteristics. Cancer Causes Control 28(4):341–349. https://doi.org/10.1007/s10552-017-0874-2
9. Merrill RM, Sloan A, Anderson AE, Ryker K (2011) Unstaged cancer in the United States: a population-based study. BMC Cancer 11:402. https://doi.org/10.1186/1471-2407-11-402
10. Polednak AP (2015) Increase in distant stage breast cancer incidence rates in US women aged 25–49 years, 2000–2011: the stage migration hypothesis. J Cancer Epidemiol 2015:710106. https://doi.org/10.1155/2015/710106