Incidence of Breast Cancer With Distant Involvement Among Women in the United States, 1976 to 2009

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Importance Evidence from the US National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database suggests that the incidence of advanced breast cancer in young women is increasing.

Objective To quantify this trend and analyze it as a function of stage at diagnosis, race/ethnicity, residence, and hormone receptor status.

Design, Setting, and Patients Breast cancer incidence, incidence trends, and survival rates as a function of age and extent of disease at diagnosis were obtained from 3 SEER registries that provide data spanning 1973-2009, 1992-2009, and 2000-2009. SEER defines *localized* as disease confined to the breast, *regional* to contiguous and adjacent organ spread (eg, lymph nodes, chest wall), and *distant disease* to remote metastases (bone, brain, lung, etc).

Main Outcome Measure Breast cancer incidence trends in the United States.

Results In the United States, the incidence of breast cancer with distant involvement at diagnosis increased in 25- to 39-year-old women from 1.53 (95% CI, 1.01 to 2.21) per 100 000 in 1976 to 2.90 (95% CI, 2.31 to 3.59) per 100 000 in 2009. This is an absolute difference of 1.37 per 100 000, representing an average compounded increase of 2.07% per year (95% CI, 1.57% to 2.58%; $P<.001$) over the 34-year interval. No other age group or extent-of-disease subgroup of the same age range had a similar increase. For 25- to 39-year-olds, there was an increased incidence in distant disease among all races and ethnicities evaluated, especially non-Hispanic white and African American, and this occurred in both metropolitan and nonmetropolitan areas. Incidence for women with estrogen receptor–positive subtypes increased more than for women with estrogen receptor–negative subtypes.

Conclusion and Relevance Based on SEER data, there was a small but statistically significant increase in the incidence of breast cancer with distant involvement in the United States between 1976 and 2009 for women aged 25 to 39 years, without a corresponding increase in older women.

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In the United States, breast cancer is the most common malignant tumor in adolescent and young adult women 15 to 39 years of age, accounting for 14% of all cancer in men and women in the age group.[1] The individual average risk of a woman developing breast cancer in the United States was 1 in 173 by the age of 40 years when assessed in 2008.[2] Young women with breast cancer tend to experience more aggressive disease than older women and have lower survival rates.[2,3] Given the effect of the disease in young people and a clinical impression that more young women are being diagnosed with advanced disease, we reviewed the national trends in breast cancer incidence in the United States.

METHODS

We obtained incidence and survival rates on women with breast cancer as of 2009 from the US Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute accessed on August 10, 2012, via SEER*Stat software version 7.1.0 and on December 2, 2012, via version 8.0.1.[4,5] The original 9 SEER registries (SEER 9)—consisting of Connecticut, Iowa, New Mexico, Utah, and Hawaii; the Indian reservations of Arizona; the metropolitan areas of Detroit, San Francisco–Oakland, and Atlanta; and 13 counties of the Seattle–Puget Sound region—have been in existence since 1973. In 1992, 4 more registries (rural Georgia, Alaskan natives, Los Angeles, and San Jose–Monterey) became available (SEER 13). For 2000-2008, 4 additional registries are available (the rest of the state of California, Kentucky, New Jersey, and Louisiana) (SEER 17). In 2012, the entire state of Georgia was added retrospectively to SEER 17 to constitute SEER 18. The SEER 9, SEER 13, and SEER 18 databases have contained information for

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9.5%, 15%, and 28% of the US population since 1975, 1992, and 2009, respectively.[6,7] For our study, we selected 1976 as the starting year to avoid the sharp uptick in early breast cancer detection that followed First Lady Betty Ford's highly publicized breast cancer diagnosis in 1974.[8]

The total number of women with malignant breast cancer during 1976-2009 with data in the SEER database, as of the 2012 release, was 936 497, of whom 197 632 were diagnosed during 1976-1991 (SEER 9), 191 779 were diagnosed during 1992-1999 (SEER 13), and 547 086 were diagnosed during 2000-2009 (SEER 18). For the 1976-2009 era, the database has data for 562 062, 288 639, 57 138, and 28 658 women with localized, regional, distant, and unstaged disease at diagnosis, respectively.

SEER*Stat was used to obtain the annual percent change (APC) and corresponding *P* values of incidence trends from the SEER databases and to perform joinpoint analyses (Joinpoint Regression Program version 4.0, National Cancer Institute).[9] The weighted least squares of year-to-year percent change end points (ie, each year during the era was included in the calculation) and age-adjusted rates were selected for the APC trends. *P* values are computed by SEER*Stat from a 2-tailed T-distribution testing the hypothesis that APC=0. We considered 2-sided *P* values less than .05 to be of statistical significance. Because the incidence trend of distant disease in young women appeared to be exponential, we also calculated incidence-rate doubling times, an intuitive and quantitative measure of the rate of increase, by dividing the log of 2 by the log of the growth rate of the exponential regression. We analyzed age at diagnosis in 5-, 10-, 15-, and 20-year intervals, each of which gave similar results. We selected the 5- and 15-year interval data for presentation, each starting at age 25 years because the incidence of breast cancer before age 25 years was too infrequent to evaluate. For the 5-year intervals, the first 2 were combined into a 25- to 34-year subgroup. For the 15-year intervals, the upper limit of the first interval (age 39 years) coincides with the upper limit used to define the young adult population.[10]

We used the SEER historic stage A definition of extent of disease at diagnosis, with *localized* referring to disease confined to the breast, *regional* to contiguous and adjacent organ spread (eg, lymph nodes, chest wall, etc), and *distant disease* to remote metastases (bone, brain, lung, etc). Stage migration was assessed by comparing each historic and unstaged disease as a function of year of diagnosis for both incidence and the number of women affected in SEER 9, using the population data reported by SEER. The association between incidence and population density was assessed by using the SEER urban-rural continuum code 2003. The SEER 13 database was used to obtain race/ethnicity and hormone receptor status, as well as metropolitan vs nonmetropolitan residence. To estimate the potential effect of the incidence increases on person-years of life affected (PYLA), we used 81.1 years as the reported expected lifespan of women in the United States[11] and individual-year-of-age incidence data from SEER 18 to determine the mean age at diagnosis in 2009 for women with metastatic breast cancer: 34.3 years for women aged 25 to 39 years and 63.5 years for women 40 years and older.[12]

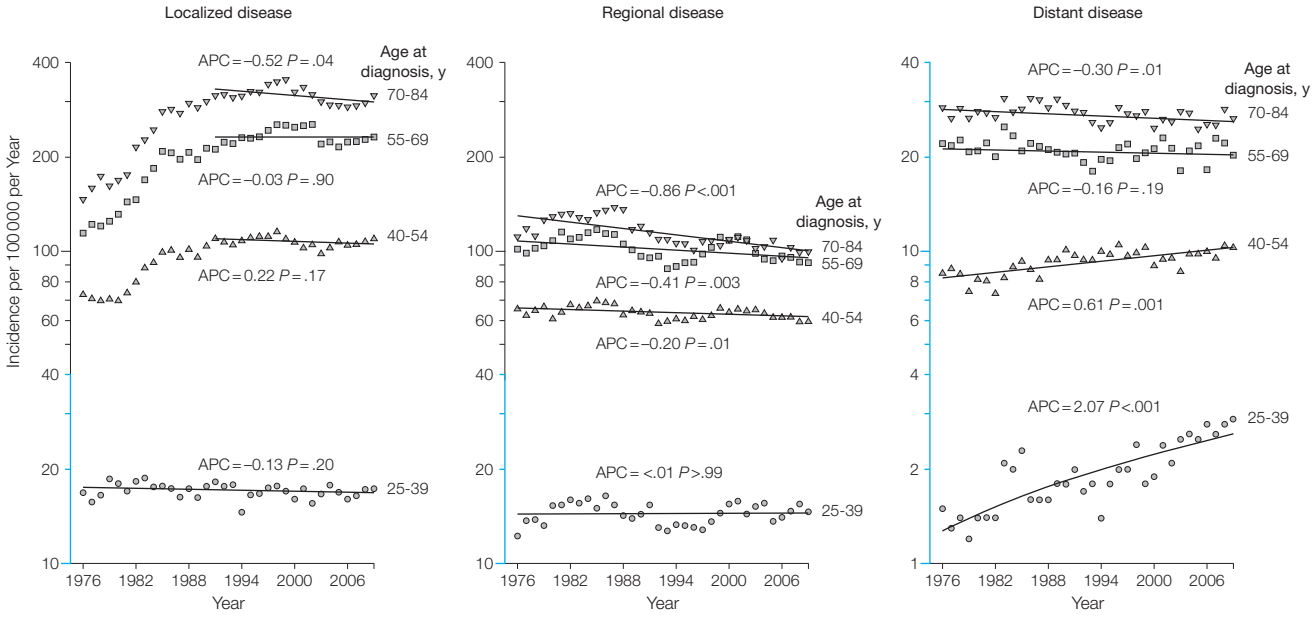
RESULTS

FIGURE 1 depicts the annual incidence rates of malignant breast cancer from 1976 to 2009 in the SEER 9 registry by 15-year age intervals and extent of disease at diagnosis. The regressions, APCs, and *P* values are for 1976-2009 except for localized disease among women aged 40 years and older among whom the era 1990-2009 was used to avoid the rapid increase in localized disease associated with the national implementation of screening mammography during prior years. Since 1976, there has been a steady increase in the incidence of breast cancer presenting with distant disease in 25- to 39-year-old women, from 1.53 (95% CI, 1.01 to 2.21) per 100 000 in 1976 to 2.90 (95% CI, 2.31 to 3.59) per 100 000 in 2009 and at an APC of 2.07 (95% CI, 1.57 to 2.58; $P<.001$). The absolute increase of 1.37 per 100 000 over 34 years is relatively small but with nonoverlapping 95% confidence intervals. There was also a statistically significant increase in the incidence of distant disease in 40- to 54-year-olds during 1976-2009, but all of their increase occurred prior to 1990 (Figure 1). No other age group had statistically significant increases, either for distant, regional, or localized disease at diagnosis, the latter in 25- to 39-year-olds throughout 1976-2009 and in women 40 years and older after the screening mammography increments.

FIGURE 2 shows the incidence of distant disease in 25- to 39-year-old women by SEER registry/era on semilog coordinates. SEER 18 data, with the largest sample size of the United States (28% of the total population) and the most recent era (2000-2009), demonstrated the steepest increase and greatest APC. SEER 13 data, with an intermediate sample size (15%) and era (1992-2009), depicted the next greatest increase and corresponding APC. SEER 9 data, with the smallest sample size (9.5%) and longest era (1976-2009), showed the slowest increase and least APC. Joinpoint analysis also revealed a continuously increasing incidence trend among 25- to 39-year-olds with no discrete inflection during 1976-2009.

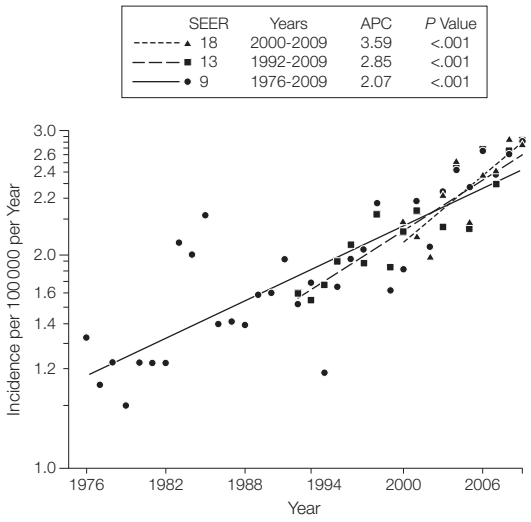
The **TABLE** lists the APCs in the rates of diagnosis of localized, regional, and distant breast cancer for 15-year age cohorts in SEER 9 for 1976-2009, SEER 13 for 1992-2009, and SEER 18 for 2000-2009. With one exception, APCs increased significantly ($P<.01$ and APC>2.0) in, and only in, women aged 25 to 39 years with distant disease at diagnosis. The one exception is in older women, who had an increase in localized disease associated with implementation of screening mammography during the 1980s. Comparing the most recent interval, 2000-2009, with the more retrograde intervals of 1975-

Figure 1. Annual Incidence of Invasive Breast Cancer in Women by 15-Year Age Intervals and Extent of Disease at Diagnosis, 1976-2009, SEER 9



Increases from 1976 through 1988 in the localized disease graph were due to national implementation of screening mammography. The regressions are logarithmic, with 1990 as the starting year for localized disease among 40-year-olds to avoid the screening mammography effect during prior years. APC indicates annual percent change; SEER, Surveillance, Epidemiology, and End Results.

Figure 2. Annual Incidence of Breast Cancer Presenting as Distant Disease in 25- to 39-Year-Old Women During 1976-2009 by SEER Registry and Era



All 3 regressions are exponential. APC indicates annual percent change; SEER, Surveillance, Epidemiology, and End Results.

2009 and 1992-2009, the annual incidence in the age group younger than 40 years accelerated over the time interval studied. The APCs in 25- to 39-year-olds increased from 2.07 (95% CI, 1.57 to 2.58) to 2.85 (95% CI, 2.09 to 3.62) to 3.59 (95% CI, 1.57 to 5.64) during 1976-2009, 1992-2009, and 2000-2009, respectively, and the corresponding estimated doubling time in the incidence rate decreased from 34 to 20 to 18 years. As another indicator of increasing frequency of distant disease, this category as a proportion of all invasive breast cancer in the age group increased from 4.4% in the 1970s to 4.8%, 5.5%, and 7.2% during the next 3 decades.

FIGURE 3 shows that the rate of increasing incidence of distant disease is inversely proportional to age at diagnosis. The greatest increase occurred in 25- to 34-year-old women, from 0.81 per 100 000 in 1976 to 2.14 per 100 000 in 2009 and at an APC of 2.24 (95% CI, 1.38 to 3.12; $P < .001$). Progressively smaller increases occurred in older women by 5-year age intervals and no statistically significant incidence increase occurred in any group 55 years or older.

For young women aged 25 to 39 years, the incidence of distant disease increased in all races/ethnicities assessed since at least 1992, when race/ethnicity became available in the SEER

Table. Annual Percent Change in the Incidence of Malignant Breast Cancer in Women by Age, Extent of Disease at Diagnosis, and Era/SEER Database

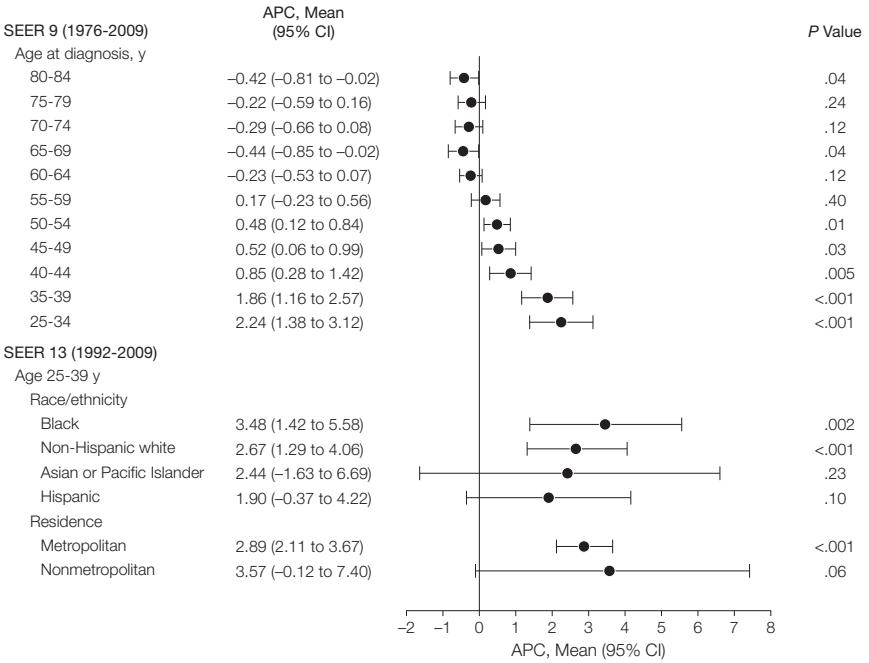
Extent of Disease	Age 25-39 y			Age 40-54 y			Age 55-69 y			Age 70-84 y		
	No.	APC (95% CI)	*P* Value	No.	APC (95% CI)	*P* Value	No.	APC (95% CI)	*P* Value	No.	APC (95% CI)	*P* Value
1976-2009/SEER 9												
Local	15 809	−0.13 (−0.33 to 0.07)	.19	81 721	1.12 (0.76 to 1.49)	<.001	110 536	1.96 (1.42 to 2.51)	<.001	91 932	1.66 (1.04 to 2.29)	<.001
Regional	13 332	0.00 (−0.29 to 0.29)	>.99	51 753	−0.20 (−0.35 to −0.06)	.01	72 265	−0.41 (−0.66 to −0.15)	.003	36 830	−0.41 (−1.11 to −0.61)	<.001
Distant	1834	2.07 (1.57 to 2.58)[a]	<.001[a]	7710	0.61 (0.37 to 0.84)	<.001	43 392	−0.16 (−0.41 to 0.08)	.19	8930	−0.30 (−0.51 to −0.09)	.01
1992-2009/SEER 13[b]												
Local	12 574	0.01 (−0.35 to 0.42)	.85	77 646	−0.25 (−0.61 to 0.12)	.17	98 737	−0.12 (−0.64 to 0.40)	.62	82 777	−0.77 (−1.34 to −0.23)	.01
Regional	10 739	0.96 (0.21 to 1.32)	.01	46 345	0.00 (−0.40 to 0.41)	>.99	42 411	0.09 (−0.65 to 0.83)	.80	27 986	−0.45 (−0.80 to −0.09)	.02
Distant	1741	2.85 (2.09 to 3.62)[a]	<.001[a]	7322	−0.12 (−0.50 to 0.27)	.52	8871	0.41 (−0.16 to 0.99)	.15	6908	−0.18 (−0.69 to 0.34)	.47
2000-2009/SEER 18[c]												
Local	13 234	0.48 (−0.17 to 1.13)	.13	91 723	0.40 (−0.09 to 0.90)	.10	120 129	−0.69 (−1.77 to 0.41)	.18	92 554	−0.69 (−1.62 to 0.25)	.13
Regional	12 291	−0.59 (−1.53 to 0.60)	.34	57 171	−1.24 (−1.50 to −0.98)	<.001	54 455	−1.84 (−2.59 to −1.03)	.001	33 777	−1.18 (−2.05 to −0.31)	.01
Distant	2081	3.59 (1.57 to 5.65)[a]	<.001[a]	9020	0.55 (−0.49 to 1.61)	.26	11 571	0.20 (−0.94 to 1.36)	.69	8354	0.17 (−0.25 to 0.60)	.38

Abbreviations: APC, annual percent change; SEER, Surveillance, Epidemiology, and End Results.
[a] APC > 2.0 and *P* < .01.
[b] SEER 13 registry began in 1992.
[c] SEER 18 registry began in 2000.

database (Figure 3). These increases were statistically significant in African American and non-Hispanic white populations, with increases from 1976 to 2009 of 3.14 to 6.25 per 100 000 and 1.52 to 2.37 per 100 000 and APCs of 3.50 (95% CI, 1.42 to 5.58; *P* = .03) and 2.67 (95% CI, 1.29 to 4.06; *P* = .01), respectively. Between 1992, when urban vs nonurban residence data became available in the SEER database, and 2009, the incidence increase appears to have occurred in both metropolitan and nonmetropolitan areas (Figure 3), with an increase of 1.77 per 100 000 in 1976 to 3.00 per 100 000 in 2009 and an APC of 2.89 (95% CI, 2.11 to 3.67; *P* < .001) for the metropolitan areas.

For 1992-2009, the APC for 25- to 39-year old women with distant disease was 8.15 (95% CI, 5.79 to 10.57; *P* < .001; 0.39 per 100 000 in 1976 to 1.21 per 100 000 in 2009) for those with estrogen receptor–positive and progesterone receptor–positive (ER+PR+) tumors. For those with ER+ and progesterone receptor–negative (ER+PR−)

Figure 3. Annual Percent Change in the Incidence of Breast Cancer Presenting as Distant Disease in Women by 5-Year Age Intervals During 1976-2009 (SEER 9) and in 25- to 39-Year-Old Women by Race/Ethnicity and Residence, 1992-2009 (SEER 13)



Error bars indicate 95% confidence intervals; APC, annual percent change; SEER, Surveillance, Epidemiology, and End Results.

tumors, the corresponding APC was 8.89 (95% CI, 6.38 to 11.46, $P<.001$; 0.09 per 100 000 in 1976 to 0.54 to 2009 per 100 000 in 2009) and for those with ER−PR+ and ER−PR−, it was −0.51 (95% CI, −4.46 to 3.59; $P=.79$; 0.09 per 100 000 in 1976 to 0.03 per 100 000 in 2009) and 5.44 (95% CI, 3.57 to 7.34; $P<.001$; 0.41 per 100 000 in 1976 to 1.03 per 100 000 in 2009), respectively.

There is no evidence for stage migration from regional, localized, or in situ categories, none of which had a decline in incidence at any time since 1976 (Figure 1, eTable 1, and eFigure, available at http://www.jama.com). Of the 5 staging categories of breast cancer available in SEER, only the unstaged group had a decline but only since 1995 whereas the increasing incidence of distant disease began no later than 1976 (Figure 1 and eFigure).

For the most recent evaluable interval in the largest SEER database (SEER 18), 2000-2004, there was an absolute difference of 55% in observed survival in 25- to 39-year-old women with distant vs locoregional disease. The mean 5-year observed survival in the age group diagnosed with breast cancer during 2000-2004 was 31.4% (95% CI, 28.4% to 34.5%) for 925 women with distant disease and 86.8% (95% CI, 86.2% to 87.4%) for 12 387 women with locoregional disease (eTable 2). In this age group, the difference between distant and locoregional disease in the 5-year survival rate (55 absolute percentage points) was greater than the survival disparity for any of the differences we identified for race/ethnicity, residence, hormone receptor status, or age at diagnosis.

Because younger patients have greater PYLA by a disease, we estimated the potential effect of the incidence increase on PYLA. Approximately 15% of the PYLA in all women with distant-disease breast cancer at diagnosis in 2008 occurred in women 25 to 39 years of age. Nearly 70% of the PYLA in 25- to 39-year-olds resulted from the increase in incidence from 1976 to 2009 (eTable 3).

COMMENT

The incidence of distant disease in women with breast cancer younger than age 40 years has been increasing at a steady or even accelerating rate, in contrast to locoregional breast cancer in the same age group and all stages of breast cancer in older women, in whom no such trend is apparent. Acceleration in the incidence of distant disease in young women is suggested by the increasing APCs, decreasing doubling times, and steeper regressions in successive SEER eras. The absolute increase of 1.37 per 100 000 over 34 years is relatively small, but the trend shows no evidence for abatement and may indicate increasing epidemiologic and clinical significance.

The increase of distant disease in young women has been independent of race and ethnicity and metropolitan vs rural residence. Non-Hispanic white and African-American individuals appear to have been more affected by the increase, as have women with the ER+ subtype of the disease.

Why is the increase occurring? One consideration must be stage migration: changes in staging classification, improvements in diagnostic imaging technology, or increasing use of imaging studies for staging and sentinel node biopsy could have over time placed patients in a higher stage group at diagnosis. For a number of reasons, however, stage migration may not explain the increasing incidence of distant disease. Stage migration may occur from an adjacent category (eg, regional to or from distant) and usually from a lower to the next higher stage category (eg, regional to distant). We could find no direct evidence for stage migration from regional, localized, or in situ disease, but this does not preclude the chance that increased diagnostic sensitivity and scrutiny is one of the reasons for our findings. Stage migration may have had a minor contribution after 1995 (eFigure) but no apparent discernible effect during the 2 decades before that, when the incidence was already occurring. Moreover, throughout the history of SEER, only a few percentage of the patients have been classified as unstaged—1% to 4% depending on the year—and therefore unstaged patients can have only a limited influence on migration into another category.

It appears that more of the increase in advanced breast cancer has been in the ER+ subtypes than in the ER− subtypes. This finding is comparatively fortunate in that breast cancer patients with distant involvement and ER+PR+ disease have a median survival of approximately 45 months vs a median survival of only 25 months for women with ER−PR− disease.[13] However, the 10-year overall survival for both groups is less than 20%. Increasing utilization of receptor testing in clinical practice is apparent in the decrease in incidence of the number of patients for whom no hormone receptor status was reported, from 0.67 per 100 000 in 1976 to 0.01 per 100 000 in 2009 and at an APC of −9.0 (95% CI, −11.75 to −6.18; $P<.001$).

A report in 2007 described an increase in the incidence of breast cancer in Geneva, Switzerland, among 25- to 39-year-olds during the 1995-2004 decade, with cancers in the age group representing 3.4% of all breast cancers in 1995 and 7.2% in 2004 ($P=.03$).[14] With only 63 patients diagnosed during the last 3 years of the decade they studied, the authors were unable to determine the stage that was most affected by the increase.

Whatever the causes—and likely there are more than 1—the evidence we observed for the increasing incidence of advanced breast cancer in young women will require corroboration and may be best confirmed by data from other countries. If verified, the increase is particularly concerning, because young age itself is an independent adverse prognostic factor for breast cancer,[2,3] and the lowest 5-year breast cancer survival rates as a function of age have been reported for 20- to 34-year-old women.[1,2] The most recent national 5-year survival for distant disease for 25- to 39-year-old women is only 31%

according to SEER data, compared with a 5-year survival rate of 87% for women with locoregional breast cancer.

Although breast cancer before age 40 years occurs in a relatively small percentage of women, the PYLA in 15- to 39-year-olds is more than one-seventh of PYLA in all women with breast cancer, and more than two-thirds of their PYLA appear to have resulted from the incidence increase. These projections add to the significance of the observed incidence increase.

In conclusion, SEER data showed a small but statistically significant increase in the incidence of breast cancer with distant involvement for women aged 25 to 39 years. The trajectory of the incidence trend predicts that an increasing number of young women in the United States will present with metastatic breast cancer in an age group that already has the worst prognosis,[1] no recommended routine screening practice, the least health insurance, and the most potential years of life. Our finding requires corroboration and, if confirmed, further study of potential causes.

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Study concept and design: All authors.
Acquisition of data: Chien, Bleyer.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Chien, Bleyer.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: All authors.
Obtained funding: Johnson.
Administrative, technical, or material support: Johnson, Chien.
Study supervision: Johnson, Bleyer.
Conflict of Interest Disclosure: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Johnson reported having served on a board for Critical Mass Young Adult Cancer Alliance and having served as a speaker at the Leukemia and Lymphoma Society AYA Survivorship Conference. Dr Bleyer reported being a consultant and speaker for Sigma-Tau Pharmaceuticals. No other disclosures were reported.
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Online-Only Material: The eTables and eFigure are available at http://www.jama.com.

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