

# The Changing Incidence of *In situ* and Invasive Ductal and Lobular Breast Carcinomas: United States, 1999-2004

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## Abstract

**Background:** National incidence rates for lobular and ductal breast cancers have not been available previously. Evidence suggests that the increased risk of breast cancer associated with combined hormone replacement therapy use is higher for invasive lobular cancers (ILC) than for invasive ductal cancers (IDC). This study provides U.S. incidence rates for these histologic types for both *in situ* and invasive cancers and assesses changes in the incidence of these cancers over time.

**Methods:** Data for this study included incident ductal and lobular breast cancer cases diagnosed from 1999 through 2004 in central cancer registries in 44 states and the District of Columbia from the National Program of Cancer Registries and the Surveillance, Epidemiology, and End Results program. We estimated incidence per 100,000 women by 10-year age groups, race, and eth-

nicity. We also assessed the percent change in invasive and *in situ* cancer incidence over time.

**Results:** We observed distinct differences in the change of incidence over time between *in situ* and invasive lobular and ductal breast cancers. The age-adjusted rates of ILC and IDC declined an average of 4.6% and 3.3% per year, respectively. Overall, ILC decreased 20.5% from 1999 to 2004. The patterns of ductal and lobular *in situ* cancer incidence were not consistent over time, and the total change was negligible.

**Conclusion:** The declines in ILC observed in our study are consistent with a decrease in cancer incidence related to a reduced use of combined hormone replacement therapy. However, other factors could also be responsible for these changes. (Cancer Epidemiol Biomarkers Prev 2009;18(6):1763-9)

## Introduction

Ductal carcinoma *in situ* (DCIS) is a heterogeneous disease defined as a neoplastic proliferation within the ductal structures of the breast (1). DCIS makes up a significant proportion of the *in situ* breast cancers diagnosed in the United States (1, 2). Risk factors for DCIS are similar to those for invasive breast cancer, including a family history of breast cancer, fewer and/or later pregnancies, older age at menopause, and increasing age (3, 4). The incidence rate for DCIS increased by a factor of 7.2 during the 1980s and began to stabilize in the 1990s (2, 5). Because DCIS is detectable using mammography (2, 3), and because the greatest increase in incidence rates occurred among women ages 50 years or older (5), the increase in DCIS incidence has been attributed, at least in part, to the increase in use of mammography (6, 7).

The clinical importance of DCIS has been a matter of considerable discussion because of the increased identification of the lesion, and although considered a precursor for invasive cancer, methods are not available to reliably

distinguish between lesions that will progress to invasive cancer and those that will not (2, 8-11). Consequently, women diagnosed with DCIS generally undergo surgical, radiation, and/or hormonal therapy. Additionally, women with a prior diagnosis of DCIS have been shown to be at higher risk of developing invasive breast cancer than women without DCIS (10, 12-14). This risk of a second primary breast cancer seems to vary by race and age at time of DCIS diagnosis (10). In at least one analysis, Black women were shown to be less likely to get radiation treatment following a lumpectomy for DCIS (15), which might explain the higher rates of recurrence and invasive cancer among this group (8, 12, 16, 17).

Although not as common as DCIS, lobular carcinoma *in situ* (LCIS) incidence rates also increased 4-fold from 1978 to 1998, with the highest increase observed among women ages 50 years and older (5). However, this increase in incidence stabilized after 1991 and was minimal after 1996 (5). LCIS was first defined as a separate entity in 1941 to differentiate it from invasive carcinoma involving the lobular structures of the breast (18). LCIS is generally considered a risk factor rather than a precursor for invasive lobular and ductal carcinomas; however, some data suggest that gene mutations in LCIS and invasive lobular carcinoma (ILC) are similar and that LCIS might be a precursor to ILC (19, 20). In addition, similar to women with DCIS, those with a diagnosis of LCIS are at an increased risk of invasive breast cancer later in life (10).

Whereas both DCIS and LCIS incidence rates increased in the 1980s and 1990s, the incidence of invasive ductal

Received 11/12/08; revised 2/13/09; accepted 4/1/09; published OnlineFirst 5/19/09.

**Note:** The findings and conclusions of the article are solely the responsibility of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the Department of Health and Human Services, or the U.S. government.

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doi:10.1158/1055-9965.EPI-08-1082

**Table 1. LCIS and DCIS breast cancer incidence rates by age group, females, United States, 1999-2004**

Age (y)	LCIS		DLCIS		DCIS		Total* <i>in situ</i> lobular, ductal and mixed	
	Cases	Rate* (95% CI) <sup>†</sup>	Cases	Rate (95% CI)	Cases	Rate (95% CI)	Cases	Rate (95% CI)
Total	28,063	3.4 (3.3, 3.4)	9,576	1.1 (1.1, 1.2)	196,244	23.2 (23.1, 23.3)	233,883	27.7 (27.6, 27.8)
<30	45	0	8	—	404	0.1 (0.1, 0.1)	457	0.1 (0.1, 0.1)
30-39	1,013	0.9 (0.8, 0.9)	237	0.2 (0.2, 0.2)	6,409	5.6 (5.4, 5.7)	7,659	6.6 (6.5, 6.8)
40-49	8,663	7.1 (6.9, 7.2)	2,429	2.0 (1.9, 2.1)	39,359	32.2 (31.8, 32.5)	50,451	41.2 (40.8, 41.6)
50-59	9,550	10.2 (10, 10.4)	3,083	3.3 (3.2, 3.4)	52,156	55.7 (55.3, 56.2)	64,789	69.3 (68.7, 69.8)
60-69	5,128	8.3 (8.1, 8.5)	2,009	3.3 (3.1, 3.4)	45,194	73.3 (72.6, 73.9)	52,331	84.8 (84.1, 85.5)
70-79	2,821	5.5 (5.3, 5.7)	1,382	2.7 (2.6, 2.9)	38,222	74.9 (74.2, 75.7)	42,425	83.2 (82.4, 84.0)
≥80	843	2.4 (2.3, 2.6)	428	1.2 (1.1, 1.3)	14,500	41.5 (40.8, 42.2)	15,771	45.1 (44.4, 45.8)

NOTE: Data from Maryland, Mississippi, North Dakota, South Dakota, Tennessee, and Virginia are not included.

\*Rates are per 100,000 women and age adjusted to the 2000 U.S. Standard Population (19 age groups—Census P25-1130).

<sup>†</sup>95% CIs were calculated using the Tiwari modification.

carcinoma (IDC) remained relatively stable from 1987 to 1999 based on the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) data (21). In contrast, ILC increased significantly over the same time period with a 1.5-fold increase overall and an even higher increase among women ages 50 years and older (21). Several studies have indicated that long-term combined estrogen and progestin hormone replacement therapy (CHRT) is associated with a 2.0- to 3.9-fold increased risk of ILC (22, 23); a much smaller increase to no increase is associated with IDC. Decline in hormone replacement therapy use after the 1990s has been postulated as one contributing cause for an overall decline in invasive breast cancer incidence rates in 2002, 2003, and 2004 (24-27). Based on the National Ambulatory and Hospital Medical Care Surveys, medical care visits for hormone replacement therapy decreased from 2000 to 2003 for both estrogen-progestin and estrogen-only hormone therapy. The largest decrease in visits was for combined estrogen-progestin therapy, which dropped from 2% of visits in 2001 to 1.3% in 2003 (28). Data from two prescription-based databases indicate that the total number of women using any type of hormone therapy in the United States dropped from 15 million in 1999 to 10 million in 2003 (29). Prescriptions for the most common oral drug brand of estrogen-progestin dropped about 66% in the time period from July 2002 to July 2003 (29).

Because studies indicate that the change in breast cancer incidence related to hormone replacement therapy (HRT) use varies between lobular and ductal cell types, this analysis provided a unique opportunity to further explore the hypothesis that recent declines in invasive breast cancer incidence at a National level were related to changes in HRT use. In addition, we were able to assess whether changes in incidence were also occurring in the most common *in situ* breast cancers. A similar analysis has not been previously published so that this study provides new information to the discussion about the relationship between HRT use and incidence of breast cancer in the United States. Previous assessments of the incidence rates for *in situ* and invasive ductal and lobular breast cancers have been based on the 9 to 11 geographic areas covered by SEER and thus have not been fully described at a national level. We used national data from state population-based cancer registries from the Centers for Disease Control and Prevention (CDC) National Program of Cancer Registries (NPCR), combined with

the SEER programs from 1999 to 2004, to provide a more detailed picture of the current incidence of LCIS and DCIS, to explore variations in histologic types over time, and to identify differences in incidence by age and race.

## Materials and Methods

Incident breast cancer cases in this study were identified from population-based cancer registries that participated in the NPCR or the SEER program. The data included cases diagnosed from 1999 to 2004 and submitted to NPCR in 2007. The NPCR and SEER registries from 44 states and the District of Columbia met case ascertainment and completeness criteria (U.S. Cancer Statistics Publication Standard<sup>3</sup>) for all 6 years and were included in the analysis. These 45 population-based registries cover 92.1% of the U.S. population. We included all female incident lobular, ductal, or mixed ductal and lobular (DL) cancers of the breast (morphology code C50.0-C50.8). Histologic diagnoses were based on the International Classification of Disease for Oncology Third Edition (ICD-O-3) codes for DCIS (8201/2, 8230/2, 8500/2, 8503/2, 8507/2, 8523/2, 8501/2), LCIS (8520/2), DLCIS (8522/2), IDC (8500/3), ILC (8520/3), and invasive ductal and lobular mixed (8522/3).

Average annual incidence rates and 95% confidence intervals (95% CI) were estimated per 100,000 women for invasive and *in situ* ductal and lobular cancers by each histologic type and combined. We estimated incidence rates by year of diagnosis for 10-year age groups, beginning at age 30 y, and by race and ethnicity. Rates were age adjusted by direct standardization to the 2000 U.S. population (19 age groups—Census P25-1130). Race was categorized as White, Black, Asian/Pacific Islander, or American Indian/Alaska Native. Linkages between central cancer registries and the Indian Health Service database were done before data submission to increase the accuracy of the American Indian/Alaska Native designation. Ethnicity was categorized as Hispanic or non-Hispanic. Race and ethnicity were not mutually exclusive.

*In situ* and invasive incidence rates were also estimated for each year to assess changes in incidence rates over time. SEER\*Stat software (30) version 6.3.6 was used to calculate incidence rates, 95% CIs, and annual percent

<sup>3</sup> <http://www.cdc.gov/cancer/npcr/uscs/2004/qa.htm#7>

**Table 2. Age-adjusted LCIS and DCIS breast cancer incidence rates by race and ethnicity, females, United States, 1999-2004**

	LCIS		DLCIS		DCIS		Total <i>in situ</i> lobular, ductal and mixed	
	Cases	Rate* (95% CI <sup>†</sup> )	Cases	Rate (95% CI)	Cases	Rate (95% CI)	Cases	Rate (95% CI)
Total	28,063	3.4 (3.3, 3.4)	9,576	1.1 (1.1, 1.2)	196,244	23.2 (23.1, 23.3)	233,883	27.7 (27.6, 27.8)
Race								
White	24,943	3.6 (3.5, 3.6)	8,496	1.2 (1.2, 1.2)	168,646	23.3 (23.2, 23.5)	202,085	28.1 (28.0, 28.2)
Black	1,643	1.9 (1.8, 2)	659	0.8 (0.7, 0.8)	17,064	20.2 (19.9, 20.5)	19,366	22.8 (22.5, 23.1)
Asian/Pacific Islander	67	1.0 (0.7, 1.2)	27	0.4 (0.3, 0.6)	596	9.4 (8.6, 10.2)	690	10.8 (10.0, 11.6)
American Indian/Alaska Native	422	1.2 (1.1, 1.3)	234	0.7 (0.6, 0.8)	6,519	19.8 (19.3, 20.2)	7,175	21.6 (21.1, 22.1)
Ethnicity <sup>‡</sup>								
Hispanic	1,304	1.8 (1.7, 1.9)	403	0.6 (0.5, 0.6)	10,376	15.3 (15.0, 15.6)	12,450	18.1 (17.8, 18.4)
Non-Hispanic	20,873	2.8 (2.7, 2.8)	7,304	1.0 (0.9, 1.0)	185,868	23.9 (23.8, 24.0)	221,433	28.6 (28.5, 28.7)

NOTE: Data from Maryland, Mississippi, North Dakota, South Dakota, Tennessee, and Virginia are not included.

\*Rates are per 100,000 women and age adjusted to the 2000 U.S. Standard Population (19 age groups—Census P25-1130).

<sup>†</sup>95% CIs were calculated using the Tiwari modification.

<sup>‡</sup>Ethnicity and race are not mutually exclusive.

change. Confidence intervals were based on the gamma method and used the Tiwari modification (31). Statistical testing for differences in incidence rates between select groups was based on the modified *F*-intervals around the rate ratio (32).

## Results

***In situ* Lobular and Ductal Carcinomas.** A total of 28,063 LCIS, 196,244 DCIS, and 9,576 DLCIS cases were diagnosed in our study population in 1999-2004. As shown in Table 1, age-specific annual average incidence rates of LCIS, DCIS, and DLCIS are all quite low before the age of 40 years. After age 39, rates of LCIS increased with age, peaking at 10.2/100,000 in women ages 50 to 59 years, then decreased steadily to 2.4/100,000 among women ages 80 years and older. In contrast, DCIS incidence rates increased steadily after age 39, peaking in women ages 70 to 79 years (74.9/100,000). Incidence rates of DCIS were about 4.5 times higher than those of LCIS at ages 40 to 49 years. This ratio increased with age, with DCIS rates being about 17 times higher than LCIS rates among women ages 80 years and older. Overall, rates for DLCIS were very low (1.1/100,000), with the highest

rates (3.3/100,000) seen among women ages 50 to 69 years.

Age-standardized rates of LCIS and DCIS by race and ethnicity are shown in Table 2. LCIS was almost twice as high among White women (3.6/100,000; 95% CI: 3.5, 3.6/100,000) than among Black women (1.9/100,000; 95% CI: 1.8, 2.0/100,000). In comparison, DCIS rates among White women (23.3/100,000; 95% CI: 23.2, 23.5/100,000) were only 1.2 times that among Black women (20.2/100,000; 95% CI: 19.9, 20.5/100,000). The incidence rate ratio of non-Hispanics to Hispanics was similar for LCIS and DCIS, 1.7 and 1.5, respectively. The lowest incidence rates for both LCIS, DCIS, and DLCIS were observed among Asian/Pacific Islanders. However, the number of cases of DLCIS was very small for this group (*n* = 27). In general, DLCIS did not uniformly follow LCIS or DCIS patterns by race.

The change in incidence rates for *in situ* breast cancer diagnoses from 1999 to 2004 is shown by year in Table 3. Over this 6-year time period, rates of LCIS varied but not in a consistent direction. The 6-year estimated annual percent change was 0.8 (95% CI: -2.1, 3.9) for LCIS, and the rate of LCIS in 2004 was almost identical to that in 1999 with a total percent change of 4.3%. Although LCIS rates peaked at 3.6/100,000 (95% CI, 3.5, 3.7/100,000) in 2002,

**Table 3. Age-adjusted LCIS and DCIS breast cancer incidence rates by year, females, United States, 1999-2004**

Year	LCIS			DLCIS			DCIS		
	Cases	Rate* (95% CI <sup>†</sup> )	Percent change	Cases	Rate* (95% CI <sup>†</sup> )	Percent change	Cases	Rate (95% CI)	Percent change
1999	4,145	3.2 (3.1, 3.3)		1,567	1.2 (1.1, 1.2)		29,803	22.1 (21.8, 22.3)	
2000	4,581	3.4 (3.3, 3.5)	6.25	1,672	1.2 (1.2, 1.3)	0.00	30,938	22.5 (22.3, 22.8)	1.8
2001	4,621	3.4 (3.3, 3.5)	0.00	1,489	1.1 (1.0, 1.1)	-8.33	33,202	23.8 (23.5, 24.0)	5.8
2002	4,993	3.6 (3.5, 3.7)	5.88	1,599	1.1 (1.1, 1.2)	0.00	33,526	23.6 (23.3, 23.8)	-0.8
2003	4,948	3.5 (3.4, 3.6)	-2.78	1,665	1.2 (1.1, 1.2)	9.09	33,700	23.3 (23.0, 23.5)	-1.3
2004	4,775	3.3 (3.2, 3.4)	-5.71	1,584	1.1 (1.0, 1.1)	-8.33	35,075	23.8 (23.6, 24.1)	2.1
Annual percent change <sup>‡</sup>		0.8 (-2.1, 3.9)			-1.7 (-4.7, 1.4)			1.3 (-0.1, 2.7)	
Total percent change			4.3		-8.7			7.9	

NOTE: Data from Maryland, Mississippi, North Dakota, South Dakota, Tennessee, and Virginia are not included.

\*Rates are per 100,000 women and age adjusted to the 2000 U.S. Standard Population (19 age groups—Census P25-1130).

<sup>†</sup>95% CIs were calculated using the Tiwari modification.

<sup>‡</sup>Annual percent change was calculated using the weighted least squares method.

**Table 4. Invasive lobular and ductal breast cancer incidence rates by age group, females, United States, 1999-2004**

Age (y)	Invasive lobular		Invasive ductal		Mixed invasive lobular and ductal		Total invasive lobular, ductal, and mixed	
	Cases	Rate* (95% CI) <sup>†</sup>	Cases	Rate (95% CI)	Cases	Rate (95% CI)	Cases	Rate (95% CI)
Total	91,951	10.6 (10.5, 10.6)	737,214	86.3 (86.1, 86.5)	76,237	8.9 (8.9, 9.0)	905,402	105.8 (105.6, 106.0)
<30	89	0.0	3,772	1.1 (1.1, 1.2)	160	0.0	4,021	1.2 (1.2, 1.2)
30-39	1,577	1.4 (1.3, 1.4)	39,646	34.2 (33.9, 34.5)	2,635	2.3 (2.2, 2.4)	43,858	37.9 (37.5, 38.2)
40-49	11,622	9.5 (9.3, 9.6)	131,219	107.3 (106.7, 107.8)	13,029	10.6 (10.4, 10.8)	155,870	127.3 (126.7, 128.0)
50-59	19,604	20.9 (20.6, 21.2)	174,673	186.6 (185.7, 187.5)	18,941	20.2 (19.9, 20.5)	213,218	227.8 (226.8, 228.8)
60-69	21,424	34.7 (34.3, 35.2)	157,729	255.7 (254.4, 256.9)	17,314	28.1 (27.6, 28.5)	196,467	318.5 (317.0, 319.9)
70-79	23,206	45.4 (44.8, 46.0)	145,919	285.6 (284.2, 287.1)	15,952	31.2 (30.7, 31.7)	185,077	362.2 (360.6, 363.9)
≥80	14,429	40.8 (40.2, 41.5)	84,256	238.4 (236.8, 240.0)	8,206	23.3 (22.8, 23.8)	106,891	302.6 (300.7, 304.4)

NOTE: Data from Maryland, Mississippi, North Dakota, South Dakota, Tennessee, and Virginia are not included.

\*Rates are per 100,000 women and age adjusted to the 2000 U.S. Standard Population (19 age groups—Census P25-1130).

<sup>†</sup>95% CIs were calculated using the Tiwari modification.

they declined during the following 2 years. Over this same time period, the 6-year estimated annual percent change for DCIS rates was 1.3 (95% CI: -0.1, 2.7). Overall, the rate was 7.9% higher in 2004 than in 1999. DLCIS rates wavered between 1.1/100,000 and 1.2/100,000 during this time period with a resulting annual percent change of -1.7 (-4.7, 1.4); however, the total number of cases was <1,700 for each year.

**Invasive Lobular and Ductal Carcinomas.** In contrast to LCIS, rates of ILC increased consistently, peaking at 45.4/100,000 (95% CI: 44.8, 46.0/100,000) among women 70 to 79 years of age and declining slightly at 80 years of age (Table 4). IDC rates increased dramatically as women entered the 40 to 49-year age group (107.3/100,000; 95% CI: 106.7, 107.8/100,000), the age at which mammography is typically first recommended. The rates of IDC also increased steadily up to age 79 years. Overall, invasive ductal, lobular, and mixed lobular and ductal breast cancers combined peaked at 362.2/100,000 (95% CI: 360.6, 363.9/100,000) among women ages 70 to 79 years.

The age-standardized incidence rates of invasive lobular and ductal breast cancers for race and ethnicity have patterns of variation very similar to those seen for *in situ* cancers (Table 5). For each of ILC, IDC, and mixed lobular and ductal cancers, the incidence rates were highest

among White women, whereas Asian/Pacific Islander women had the lowest rates of invasive ductal and lobular cancers, except in the case of ILC of which the rates overlapped those observed in American Indian/Alaska Native women. As with the *in situ* cancers, incidence rates of invasive cancers were higher among non-Hispanics than among Hispanics.

We assessed the change in incidence rates over time for invasive lobular and ductal cancers separately and combined, and for all invasive breast cancers for comparison (Table 6). Rates of both invasive lobular and ductal breast cancers decreased from 1999 to 2004. However, the total percent decrease from 1999 to 2004 was greatest for ILC (-20.5%) over this time period. In addition, the annual percent change was greatest for ILC (-4.6%; 95% CI: -5.8, -3.4) as well. There was no decrease in rates for IDC from 2003 to 2004 despite the decreases observed in previous years. The annual percent change over the entire time period for IDC was -3.3% (95% CI: -4.2, -2.5). For total invasive lobular and ductal breast cancers, the annual percent change was -3.0 (95% CI: -3.6, -2.3), and the total percent change over this time period was -12.8. For all invasive breast cancers of any histologic type, the annual percent change was -2.5% (95% CI: -3.6, -1.5), and the total percent change over this time period was -11.6.

**Table 5. Age-adjusted lobular and ductal invasive breast cancer incidence rates by race and ethnicity, females, United States, 1999-2004**

	Invasive lobular		Invasive ductal		Mixed invasive lobular and ductal		Total invasive lobular, ductal, and mixed	
	Cases	Rate* (95% CI) <sup>†</sup>	Cases	Rate (95% CI)	Cases	Rate (95% CI)	Cases	Rate (95% CI)
Total	91,951	10.6 (10.5, 10.6)	737,214	86.3 (86.1, 86.5)	76,237	8.9 (8.9, 9.0)	905,402	105.8 (105.6, 106.0)
Race								
White	84,045	11.2 (11.1, 11.3)	639,864	87.5 (87.3, 87.7)	68,888	9.4 (9.3, 9.5)	792,797	108.1 (107.9, 108.3)
Black	5,444	6.6 (6.4, 6.8)	66,566	77.5 (76.9, 78.1)	4,423	5.2 (5.1, 5.4)	76,433	89.3 (88.7, 90.0)
Asian/Pacific Islander	261	4.4 (3.9, 5.0)	2,757	43.7 (42.0, 45.4)	204	3.2 (2.7, 3.7)	3,222	51.3 (49.5, 53.2)
American Indian/ Alaska Native	1,150	3.6 (3.4, 3.9)	19,382	58.9 (58.0, 59.7)	1,841	5.6 (5.3, 5.8)	22,373	68.1 (67.2, 69.0)
Ethnicity <sup>‡</sup>								
Hispanic	3,966	6.2 (6.0, 6.4)	42,324	61.3 (60.7, 61.9)	4,383	6.4 (6.2, 6.6)	50,673	73.9 (73.2, 74.5)
Non-Hispanic	87,985	10.9 (10.8, 11.0)	694,890	88.5 (88.3, 88.7)	71,854	9.1 (9.0, 9.2)	854,729	108.5 (108.3, 108.7)

NOTE: Data from Maryland, Mississippi, North Dakota, South Dakota, Tennessee, and Virginia are not included.

\*Rates are per 100,000 women and age adjusted to the 2000 U.S. Standard Population (19 age groups—Census P25-1130).

<sup>†</sup>95% CIs were calculated using the Tiwari modification.

<sup>‡</sup>Ethnicity and race are not mutually exclusive.

**Table 6. Age-adjusted lobular and ductal invasive breast cancer incidence rates by year, females, United-States, 1999-2004**

Year	Invasive lobular			Invasive ductal			Total invasive lobular, ductal, and mixed			All invasive breast cancers		
	Cases	Rate*	Percent change	Cases	Rate	Percent change	Cases	Rate	Percent change	Cases	Rate	Percent change
1999	16,226	11.7		128,613	94.0		155,425	113.4		183,501	133.4	
2000	16,174	11.4	-2.6	127,420	91.7	-2.4	155,581	111.8	-1.4	182,769	130.9	-1.87
2001	15,673	10.9	-4.4	123,004	87.2	-4.9	151,854	107.5	-3.9	185,044	130.5	-0.31
2002	15,431	10.6	-2.7	121,181	84.5	-3.1	150,402	104.7	-2.6	183,572	127.3	-2.45
2003	14,456	9.7	-8.5	117,522	80.7	-4.5	145,440	99.6	-4.9	175,959	120.1	-5.66
2004	13,991	9.3	-4.1	119,474	80.7	0	146,700	98.9	-0.7	175,501	117.9	-1.83
Annual percent change <sup>†</sup>	-4.6 (-5.8, -3.4) <sup>‡</sup>			-3.3 (-4.2, -2.5)			-3.0 (-3.6, -2.3)			-2.5 (-3.6, -1.5)		
Total percent change	-20.5			-14.2			-12.8			-11.6		

NOTE: Data from Maryland, Mississippi, North Dakota, South Dakota, Tennessee, and Virginia are not included.

\*Rates are per 100,000 women and age adjusted to the 2000 U.S. Standard Population (19 age groups—Census P25-1130).

<sup>†</sup>Annual percent change was calculated using the weighted least squares method.

<sup>‡</sup>95% CIs were calculated using the Tiwari modification.

## Discussion

We provide the first population-based analysis of data representing 92.1% of the U.S. population for *in situ* and invasive lobular and ductal breast cancer incidence for years 1999-2004. The use of data from the NPCR and SEER combined allowed us to provide truly national data by age and race. Because we were able to assess rates separately for ductal versus lobular breast cancer, our results provide further insight into the potential role of HRT in the recent decline of breast cancer in the United States. We also evaluated whether changes in incidence were also occurring in the most common *in situ* breast cancers.

Based on SEER data alone, Li et al. (5) reported a 7-fold increase in DCIS rates in the nine participating regions from 1980 to 2001 with a 1.1% total increase from 1997 to 2001. Our data indicate an annual percent change of 1.3% for DCIS from 1999 to 2004 and a total increase of 7.9% over this time period, although a decrease was observed in 2002 and 2003. An increase in mammography use was likely linked to the large increase in DCIS diagnoses in the 1980s and 1990s given that mammography use increased by 140% from 1987 to 2000 (33). However, we cannot eliminate the possibility of a real increase in incidence regardless of the potential increased detection through mammography use. Ideally, the increased detection of DCIS through mammography will decrease the invasive cancers diagnosed in later years, with the size of the decrease dependent on the proportion of DCIS that would have progressed to invasive disease. This potential decrease, however, could be masked by changes in risk factors and incidence of invasive cancers. The reason for the decrease of DCIS in 2002 and 2003 is not clear. Although a decrease in mammography use was observed between 2000 and 2005 using data from both the Behavioral Risk Factor Surveillance System (34) and the National Health Information Survey (35), it was not likely the reason for the decrease in incidence because the rates of DCIS actually increased in 2004.

LCIS is not detected directly through mammograms, but it can be incidentally detected with an increase in biopsies resulting from the use of mammography. Li et al. (5) reported a 2.6-fold increase in LCIS rates from 1980 to

2001, but with a smaller increase in rates after 1991. However, there was little noticeable change in LCIS rates in our study, with an annual average increase noted of 0.8% and only a 4.3% increase in rates over the total time period studied.

The pattern over time is markedly different in invasive versus *in situ* breast cancer. The age-adjusted rate of all invasive breast cancers combined decreased by 11.6% from 1999 to 2004, with the largest drop seen among invasive lobular cancers, which declined an average of 4.6% per year. Based on SEER data alone, incidence rates of invasive lobular and ductal breast cancers were reported to have increased 1.5-fold between 1987 and 1999 (10, 21). Recently published analyses of incidence data showed a drop in invasive breast cancer rates beginning in mid-2002 (25-27). Our data also indicated a recent decrease in invasive lobular and ductal carcinomas. However, the largest percent decline was seen in 2003 for ILC cancers with an 8.5% drop in age-adjusted rates for that year. Invasive ductal and mixed ductal-lobular cancers also declined in 2003. In 2004, no decrease was observed for ductal cancers and little change occurred for mixed cancers (-0.7%); however, ILC continued to decrease (-4.1%). Based on our data, a large portion of the decrease in overall breast cancer incidence in 2003 was likely related to the decrease in invasive lobular cancers.

Decreases in mammography use and declines in the use of CHRT have both been postulated as a cause for the decrease in overall breast cancer incidence in 2002 (22, 24-26, 36-38). However, unlike ductal carcinoma, lobular breast cancer is not detected primarily through mammography. There is growing evidence that the increased risk of breast cancer associated with CHRT use is higher for invasive lobular and invasive lobular-ductal mixed tumors than for invasive ductal carcinoma (22, 23). Therefore, our findings are more consistent with a decrease in cancer incidence related to a reduced use of CHRT than with a decrease in mammography use. However, other factors could also be responsible for the change in incidence we observed. For example, the increased detection of DCIS in the 1980s and 1990s could have led to a decrease in invasive cancers in subsequent years.

The incidence data in this analysis represent the most complete analysis of lobular and ductal breast cancers conducted to date. However, data from six states are not included. The exclusion of these data may have influenced the reported incidence rates. In addition, misclassification between histologic types of breast cancer or between *in situ* versus invasive breast cancers may have occurred. However, we did not analyze subtypes of DCIS and LCIS, which are likely more prone to misclassification between categories. Although we used data that had been linked to the Indian Health Service databases to improve the classification of American Indian/Alaska Native populations, some misclassification of this and other races likely remains.

Our data indicate changing incidence patterns that differ from those previously reported for invasive and *in situ* lobular and ductal breast cancers. We identified variations in rates between the cancer histologic types by age and over time. The patterns of DCIS and LCIS have not been consistent from year to year, and overall, little change has occurred from 1999 to 2004. In contrast, invasive lobular and lobular-ductal mixed breast cancers have consistently decreased. Invasive ductal cancer decreased from 2000 to 2003; however, the rates leveled off in 2004. A large proportion of the recently reported decrease in overall invasive breast cancer rates was likely related to the decrease in lobular histologies. These cancer types are more sensitive than ductal types to the effects of CHRT use, which would suggest an association with the decrease in CHRT use. Breast cancer rates should continue to be monitored over time, as well as the histologic type, to assess whether the decrease in incidence continues and whether the decrease remains consistent with the reduction in CHRT use. Despite the observed decrease in breast cancer incidence, breast cancer screening through mammography remains vitally important in reducing the incidence of invasive breast cancer in the U.S. population. Given that a significant proportion of women are still not receiving regular mammography screening, the public health community should investigate new strategies and implement proven interventions for increasing mammography screening.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Acknowledgments

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We thank the state and regional cancer registry staff who collected the data used in this study.

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