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Incidence of Ductal Carcinoma in Situ in the United States, 2000-2014

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Abstract

Background.—In absence of definitive molecular risk markers, clinical management of patients diagnosed with ductal carcinoma in situ (DCIS) remains largely guided by patient and tumor characteristics. In this study, we analyzed recent trends in DCIS incidence and compared them against trends in mammography use.

Methods.—The Surveillance, Epidemiology and End Results (SEER) registry was queried for patients diagnosed with DCIS from 2000 to 2014 (18 registries). Joinpoint regression analyses were used to compute age- and race-stratified trends in age-adjusted incidence of DCIS. The patterns of DCIS incidence were compared against mammography utilization data from the National Health Interview Survey.

Results.—Between 2000 and 2014, overall DCIS incidence in the US population was stable (P=0.24). Among age groups 20–44 years and 45–55 years DCIS incidence increased by 1.3% (P=0.001) and 0.6% (P=0.02) per year, respectively. While stable among white women, DCIS incidence increased among black women and women of other races by 1.6% (P<0.001) and 1.0% (P=0.002) per year, respectively. Mammography uptake correlated well with DCIS incidence, with the exception of women aged 40–49 years and black women who experienced an increase in DCIS incidence despite stagnating and decreasing mammography uptake, respectively.

Conclusions.—Overall DCIS incidence rates have remained stable between 2000 and 2014. However, subgroup analyses revealed an increase in incidence among both younger women and black women.

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Conflicts of interest.
None to disclose.

Impact.—DCIS incidence trends did not correlate with the mammography uptake patterns, suggesting that etiologic factors other than screening may be leading to an increased DCIS incidence in these groups.

INTRODUCTION

The introduction of mammographic screening in the early 1980s has led to a dramatic increase in the detection of ductal carcinoma in situ (DCIS) over the past three decades (1,2). In the United States, more than 50,000 women are diagnosed with DCIS each year and DCIS accounts for an estimated 18–25% of the total number of newly diagnosed breast tumors (3).

Consisting of a heterogeneous group of pre-invasive neoplastic lesions, DCIS is primarily characterized by clonal proliferation of malignant cells that are confined to the lumen of breast ducts and lobules (4). The phenotypic spectrum of DCIS ranges from indolent and slowly growing disease to fast growing, aggressive subtypes that can quickly invade the surrounding stroma and metastasize to distant organs (5,6). However, due to a lack of reliable prognostic markers that delineate the different risk groups, the vast majority of patients undergo invasive treatment in the form of surgery, either alone or in combination with radiation and hormone therapy (7). To enable effective and personalized management of DCIS patients, there is an ongoing effort to identify clinical and biologic markers that predict the propensity to progress to invasive cancer (8). As a more concise picture of patient-specific risk profiles is bound to emerge, it becomes necessary to characterize the potential impact of risk-stratified management strategies at the population level. In particular, a better understanding of subtype-specific incidence patterns by age and race will inform cost-effectiveness analyses and the estimation of overdiagnosis rates in the population.

In this study, we analyzed data from the US population-based cancer registry SEER to characterize recent trends in (i) DCIS incidence by age and race, and (ii) the distribution of disease subtypes among patients diagnosed with DCIS. Because DCIS is a primarily screen-detected disease, we further compared the incidence trends against uptake of mammography screening.

METHODS

SEER data

Women diagnosed with DCIS in the United States between 2000 and 2014 were identified through the population-based cancer registries that participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER), which represents approximately 28% of the U.S. population (9). Women aged 20 years or older were included if diagnosed with behavior code ICD-O-3 "in situ" and one of following histology codes for DCIS: 8050, 8140, 8200, 8201, 8211, 8230, 8246, 8260, 8343, 8401, 8480, 8481, 8490, 8500, 8501, 8503, 8504, 8507, 8508, 8521, 8522, 8523, 8543, or 8550. Patients without microscopic confirmation of the diagnosis, those identified at autopsy or on death certificate

only, and patients for whom DCIS was not the first cancer diagnosis were excluded from analyses. Ethics approval for this study was obtained from Duke University.

Patient-specific variables included age at diagnosis (20–44 years, 45–54 years, 55–69 years and 70 years or older), race (white, black, other, unknown), and year of diagnosis (2000–03, 2004–07, 2009–11, and 2012–14). Tumor-specific variables included nuclear grade (low, intermediate, high, unknown), tumor size (≤10mm, 11–30mm, >30mm, unknown), estrogen receptor (ER) and progesterone receptor (PR) status (positive, negative, unknown). In addition to race- and age-specific subgroups, we further defined a subgroup of "low-risk" DCIS patients based on the eligibility criteria of the COMET active surveillance trial (10). Patients were included in this subgroup if they were 40 years or older at diagnosis and had an ER- or PR-positive lesion of low or intermediate nuclear grade.

To evaluate the long-term relationship between mammography screening and DCIS incidence, we compared crude mammogram rates (see below) to the corresponding crude DCIS incidence rates over the extended interval from 1992 to 2014 (SEER, 13 registries).

Mammography data

Mammography utilization data for women aged 40 years or older was obtained from the National Health Interview Survey (NHIS) (11). More precisely, we used the fraction of women who self-reported having had a mammogram in the two years prior to the survey round as a proxy for mammogram uptake. To include a historical perspective on mammography uptake data we included survey rounds from 1987, 1993, 1994, 2000, 2005, 2008, 2010, 2013 and 2015. The age-unadjusted (crude) rates were further stratified by age category (40–49, 50–64 and ≥65 years) and race (black and white).

Statistical Analyses

SEER*Stat software version 8.34 (National Cancer Institute, Bethesda, MD, released March 22, 2017) was used to calculate age-adjusted DCIS incidence rates from 2000 to 2014 using the SEER 18 database. Rates were age-adjusted to the 2000 U.S. standard population. The magnitude and direction of DCIS incidence trends by grade, ER status, PR status and tumor size were evaluated using the Joinpoint Regression Program version 4.5.0.1 (National Cancer Institute, Bethesda, MD, released June 2017). This program uses permutation analysis to fit a series of joined straight lines on a logarithmic scale to observed rates and estimate the annual percent change (APC). The study period was divided into intervals 2000–2003, 2004–2007, 2008–2011, and 2012–2014, and associations between time intervals and patient and tumor characteristics were evaluated using χ^2 tests. Trends in the proportion of specific tumor subtypes between 2000 and 2014 were evaluated using Cochrane-Armitage tests.

Crude screening rates from the NHIS survey (1987–2015) were plotted alongside crude DCIS incidence rates (SEER 13, 1992–2014), stratified by race and age groups, and trends in crude DCIS incidence and mammography uptake rates were evaluated using Kendall's tau correlation test, separately for the time periods 1992–1999 and 2000–2014.

All *P*-values were calculated as two-sided, with statistical significance declared for *P*-values below 0.05. Unless otherwise stated, statistical analyses were performed in statistical software SAS version 9.4 (SAS Institute Inc, Cary, NC).

Interactive Visualizations

Trends in age-adjusted DCIS incidence for different combinations of age, race and tumor features (nuclear grade, tumor size, ER and PR status) are presented in an online supplementary in the form of an interactive web-page. The visualizations were created using Tableau software (version 9.1, Tableau Software Inc, Seattle, WA): https://public.tableau.com/profile/yiling.liu#!/vizhome/tableau_new_0/Story1?publish=yes.

Incidence and mortality of colorectal, cervical and female breast cancer

To provide a broader context for our findings, we compared the US incidence and mortality rates of female breast, colorectal and cervical cancers between 1999 and 2015. Annual incidence and mortality rates were obtained from the U.S. Cancer Statistics Data Visualizations Tool (12). Relative rates were obtained by rescaling the absolute rates with respect to the corresponding baseline rates from 1999.

RESULTS

Between 2000 and 2014, 145,670 women with DCIS met the inclusion criteria. Demographic and clinicopathologic characteristics of the study population are summarized in Table 1. The majority of diagnoses were recorded in white women (n=113,396, 77.8%), followed by black women (15,712, 10.8%) and women of other races (15,112, 10.4%).

DCIS incidence trends

While the overall DCIS incidence rate remained stable between 2000 and 2014 (*P=0.24*, Figure 1A), significant changes were observed for specific subgroups. When stratified by race (Figure 1B), DCIS incidence rates increased among black women and women of other races by 1.6% (*P*<0.001) and 1.0% (*P*=0.002) per year, respectively. In an age-stratified analysis (Figure 1C), incidence rates increased among women of ages 20–44 years and 45–54 years by 1.3% (*P*=0.001) and 0.6% (*P*=0.02) per year, respectively. Among women of ages 55–69 years, the incidence rates trended downward by 0.3% per year (*P*=0.08).

DCIS tumor characteristics at diagnosis

The proportions of incident DCIS cases with unknown grade, unknown ER and PR status and unknown size decreased drastically between 2000 and 2005, and then continued to decrease at a slower rate until 2014 (Figure S1). During the period 2000–2003, 82.5% of women had unknown ER status, 83.7% had unknown PR status, 24.7% had unknown grade, and 38% had unknown tumor size (Table 1). By 2012–2014, these proportions had decreased to 6.9%, 12.4%, 10.0%, and 19.0% respectively.

Among newly diagnosed cases with known tumor characteristics, the distributions of nuclear grade, tumor size and hormone receptor status underwent significant changes (Figure 2 and online materials). With respect to hormone receptor status, the proportions of both ER and

PR positive tumors increased significantly ($P<0.001$ for both, Figure 2A). While there was no measurable trend among grade I tumors, the proportions of grade II and grade III tumors increased and decreased, respectively ($P<0.001$, Figure 2B). Finally, the proportion of small tumors (1–10mm) decreased ($P<0.001$) while the proportion of tumors larger than 30mm increased ($P<0.001$); there was no measurable trend among tumors of size 11–20 mm (Figure 2C). Changes in tumor characteristics for different age- and race-groups are found in Figure 3 and online materials. While the trends among white women (Figure 3A) mirrored those of the overall population (Figure 2), differential trends were found in black women (Figure 3B). First, the proportion of grade I tumors decreased among black women ($P<0.05$) while being stable among white women. Second, there were no noticeable trends in the tumor size distributions among black women, in contrast to the observed shift from smaller (≤1cm) to larger (>3cm) tumors in white women.

During the most recent time period from 2012 to 2014 (Table 2, Supplementary Table S1), 14.3% of DCIS patients with known tumor grade had a grade I lesion, 43.4% a grade II lesion, and 42.3% a grade III lesion. Among women with known ER status, 87.5% had an ER-positive lesion and 12.5% an ER-negative lesion. Among lesions of known size, 46.6% were 1–10 mm, 37.5% were 11–30 mm, 14.4% were larger than 30 mm, and 1.5% were micro-invasive. Among patients with known tumor grade and ER or PR status, the proportion of women who satisfied the criteria of the low-risk subgroup (age ≥40 years with grade I/II and ER- or PR-positive tumor) increased from 47.2% (2000–2004) to 52.5% (2012–2014) ($P<0.001$).

Mammography utilization and DCIS incidence

To provide historical context, we performed a comparison of mammography utilization and DCIS incidence over an extended time period. Prior to 2000, both DCIS incidence and self-reported mammography uptake increased among all age groups and races (Figure 4, $P<0.01$ for all subgroups). After 2000, more complex patterns emerged. Among women aged 40–49 years (Figure 4A), DCIS incidence continued to increase ($P=0.015$) while mammography uptake decreased ($P=0.01$). Among women aged 50–64 (Figure 4B), both mammography uptake and DCIS incidence decreased ($P=0.01$ and $P=0.004$). Screening uptake and DCIS incidence were stable among women of age 65 years and older (Figure 4C). Among black women of all ages (Figure 4D), we found that the DCIS incidence continued to increase during the period 2000–2014 ($P<0.0001$) despite unchanged mammogram use ($P=0.9$). Among white women, mammogram use decreased ($P=0.006$) yet there was no accompanying downward trend in DCIS incidence ($P=0.2$).

Incidence and mortality of colorectal, cervical and female breast cancers

The relative US incidence and mortality rates of colorectal, cervical and female breast cancers between 1999 and 2015 are shown in Figure 5. While mortality rates consistently decreased in all three cancer sites, a concurrent decrease in incidence was only observed in colorectal and cervical cancers; the incidence rate of female breast cancers remained unchanged after 2005.

DISCUSSION

It is well established that widespread mammographic screening has resulted in a marked increase in DCIS detection since the mid-1980s (13–15). In this study we found that the overall incidence rate of DCIS has now stabilized between 2000 and 2014. However, we noted an unanticipated discrepancy between breast cancer screening and incidence rates of DCIS in some groups. NHIS survey data have shown that between 2000 and 2008, the age-adjusted rate of breast cancer screening among women aged 40–49 and 50–64 years fell by 2.7% and 4.4%, respectively (16). Paradoxically, our analysis shows that the incidence rates of DCIS have in fact *increased* among women of ages 20–44 years and 45–54 years (1.3% and 0.6% per year respectively; $P<0.05$ for both). The increase in DCIS incidence among women 20–44 is especially notable, as most of these women are younger than the age at which screening is recommended. Moreover, although screening rates have not markedly changed among blacks, the DCIS incidence rate is disproportionately increasing in this group as well (1.6% annually, $P<0.05$). This divergence between DCIS incidence rate and breast cancer screening rate has not been previously observed and suggests an effect in some groups of either endogenous or environmental risk factors for DCIS that have not yet been recognized or identified (17,18).

We found that the biologic characteristics of DCIS and relationship to screening prevalence could not be easily determined, as many DCIS features were not reported prior to 2000. Between 2000 and 2014, reporting of histopathologic tumor features in the cancer registry SEER increased substantially, at least partly due to evolving coding guidelines and practices of the cancer registry. In particular, the fraction of cases with unknown ER status decreased from 84% (2000–2003) to 7% (2012–2014). This change has been attributed to increased ER testing after FDA approval of Tamoxifen for DCIS in 2000 (19).

However, among cases with known tumor features, we noted changes in the distribution of tumor size, grade and hormone receptor status. As there is little evidence to suggest a reporting bias, these observations likely represent real underlying trends. The most marked change was noted in hormone receptor status, with an increase in the fraction of ER-positive DCIS from 80% in 2000 to 87% in 2014. In contrast, it has been reported that the incidence rate of ER-positive invasive cancers fell during this period, while the incidence of ER-negative invasive cancers did not change significantly (20). This finding has been widely attributed to a lower rate of exogenous hormone use resulting in fewer women being exposed to the proliferative effects of combined estrogen plus progestin on the breast epithelium (21). The disproportionate rise in ER-positive, and not ER-negative DCIS during a time interval when use of exogenous hormones dropped, again suggests that etiologic risk factors for DCIS and invasive cancer may differ.

Comparing screening prevalence and DCIS incidence against invasive breast cancer incidence and mortality provides insights into the respective roles of screening and treatment in prevention. Over the past decade, breast cancer mortality has dropped substantially while invasive cancer incidence remained stable after 2003 (Figure 5A). These trends, in conjunction with relatively stable screening uptake and DCIS incidence patterns (Figure 1A, Figure 4), make it difficult to attribute more than a negligible impact of DCIS detection and

treatment on recent breast cancer mortality reductions and suggest a larger effect of treatment improvements on reducing breast cancer mortality (22). This observation stands in contrast to other cancers, such as cervical (Figure 5B) and colorectal cancer (Figure 5C), for which effective screening programs have successfully reduced both incidence and mortality.

A limitation of this study is the use of self-reported mammography utilization data. Indeed, prior studies have suggested that self-reported data overestimate the true utilization rate, and the degree of overestimation varies by age and race (23). However, because we used these data to estimate relative trends only, the impact of potential systematic reporting biases is unlikely to affect our conclusions. Another limitation is that the study populations for cancer incidence (SEER) and mammography utilization (NHIS) are not identical. This limitation is partially addressed by the fact that both the NHIS survey and SEER registry draw from samples that are representative of the US population.

Finally, we note that during the most recent study period (2012–2014), the majority of DCIS lesions diagnosed were of low to intermediate nuclear grade (58%) and ER positive (87%). In particular, 55% of newly diagnosed DCIS patients satisfied the three main criteria for low-risk DCIS as used by the ongoing COMET trial which randomizes patients with DCIS to either usual care or active surveillance (10): age ≥40 years, nuclear grade I/II and hormone receptor-positive. Therefore, should active surveillance become part of usual care, a sizable fraction of DCIS patients may have the option to de-escalate treatment and delay surgery unless there is progression to invasive cancer.

In an era of increasingly tailored treatment options for cancer patients, it is essential to gain a clear understanding of the different disease subtypes and their incidence patterns by age and race groups. For this reason, we developed a web-based visualization tool that enables the user to explore the complex incidence patterns for DCIS during the period from 2000 to 2014 (see Methods section for details). Altogether, the results of this study data provide the basis for future cost-effectiveness studies and other model-based research activities for DCIS.

In conclusion, we observed an emerging divergence between DCIS incidence and mammographic screening patterns in some subgroups. Specifically, we found an increase in ER-positive DCIS and DCIS diagnosed in young patients and among African American individuals. Importantly, these trends did not correlate with the mammography uptake patterns, suggesting that etiologic factors other than screening may be leading to an increased DCIS incidence in these groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation list:

DCIS	ductal carcinoma in situ
SEER	Surveillance, Epidemiology and End Results registry
ER	estrogen receptor
PR	progesterone receptor
NIHS	National Health Interview Survey

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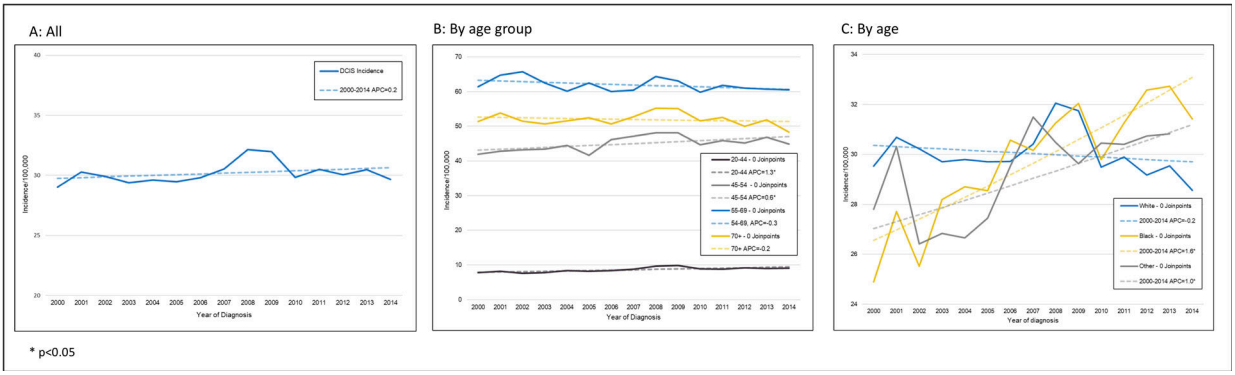

Figure 1: Age-adjusted DCIS incidence trends, overall and by age and race

Annual percentage change (APC) in the DCIS incidence rate in the United States, 2000–2014, overall (A), by race (B) and age group (C). Carat (^) indicates that the APC is statistically significantly different from zero (P<0.05). In order to highlight trends, the scales of the y-axes vary.

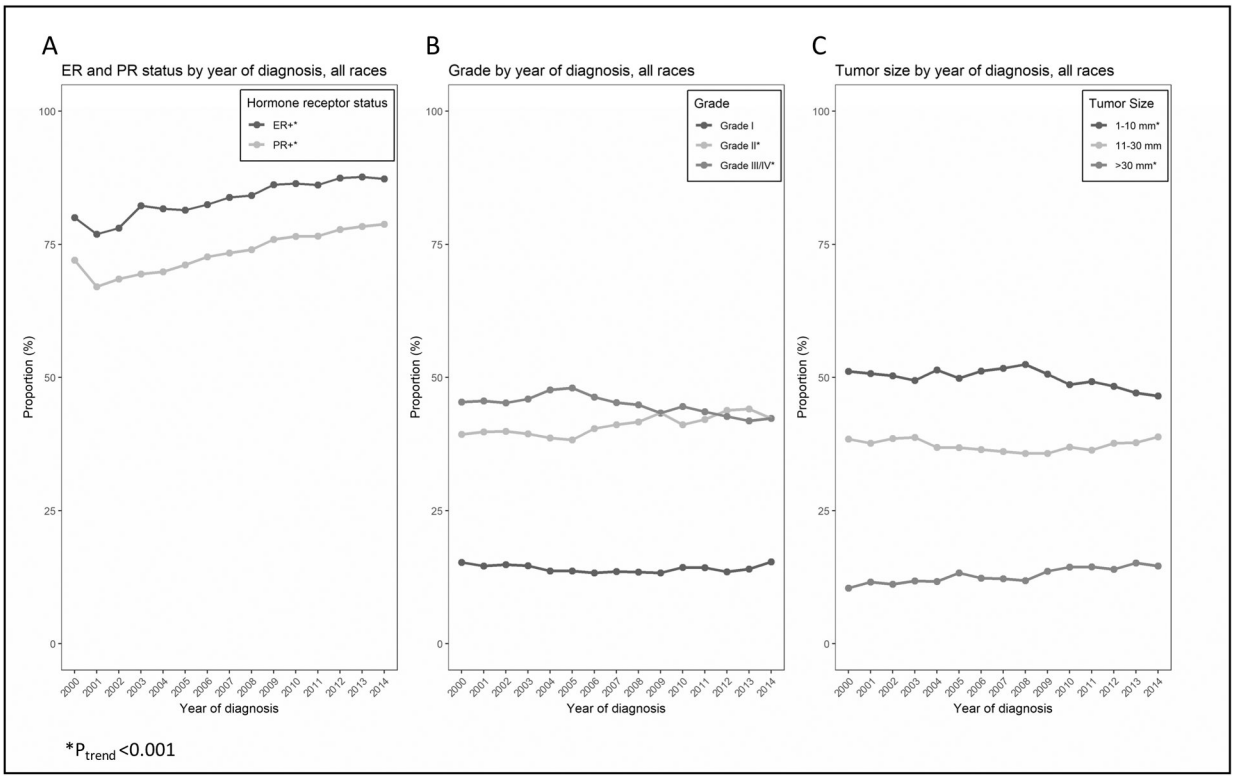

Figure 2: Trends in tumor characteristics among women diagnosed with DCIS

Proportions of women diagnosed with ER-positive and PR-positive DCIS (A), grade I, II and III DCIS (B), and small (1mm-10mm), intermediate (11mm-30mm) and large (>30mm) DCIS (C) in the United States, 2000–2014. Only cases with known tumor features are included in the analyses.

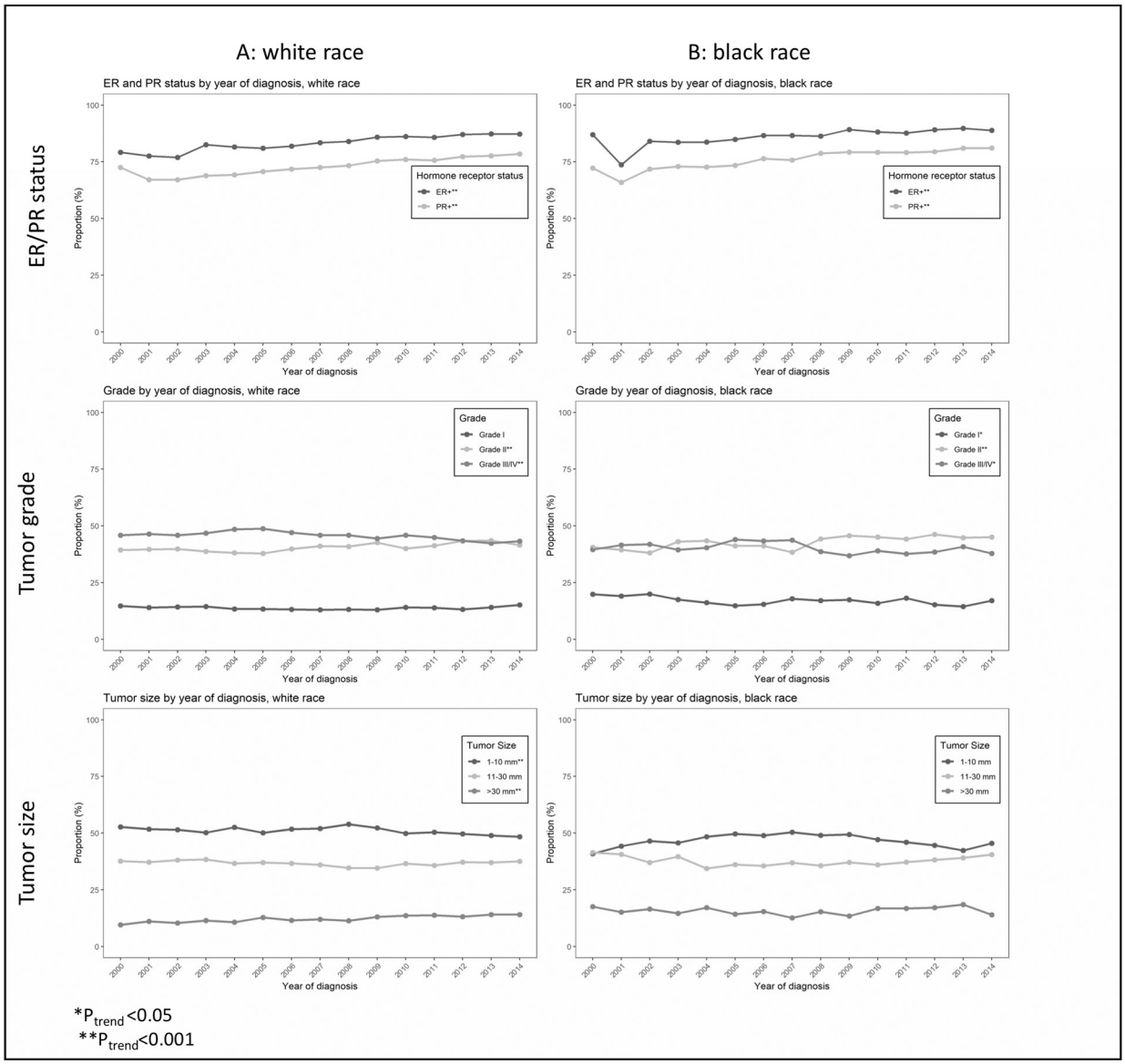

Figure 3: Trends in tumor characteristics among women diagnosed with ductal carcinoma in situ (DCIS); subgroup analyses

Proportions of women diagnosed with estrogen receptor (ER) positive and progesterone (PR) positive DCIS, grade I, II and III DCIS, and small (1mm-10mm), intermediate (11mm-30mm), large (>30mm) DCIS among white women (A) and black women (B), in the United States, 2000–2014. Only cases with known tumor features are included in the analyses.

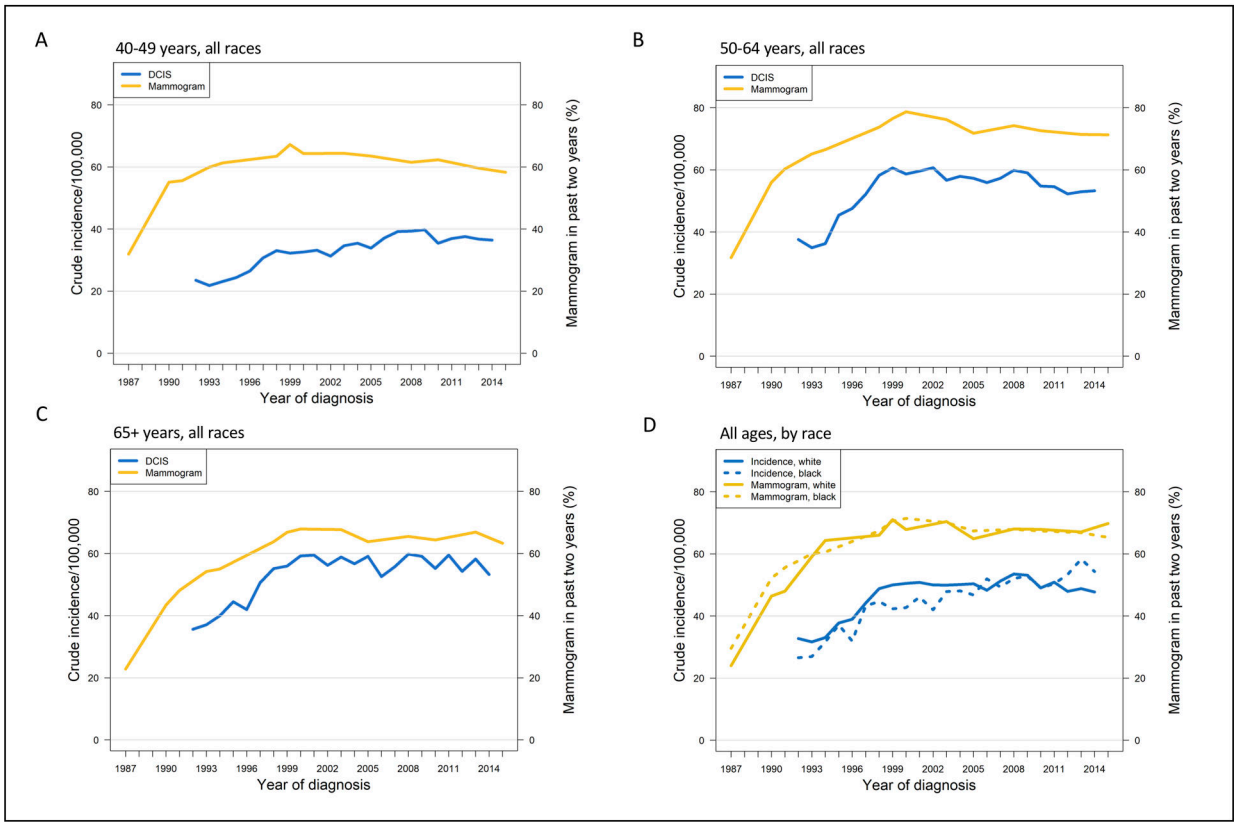

Figure 4: Mammogram utilization (1987–2015) and DCIS incidence (1992–2014), by age groups and race

Crude mammogram utilization (NIHS data) and DCIS incidence (SEER 13) rates among women of all races aged 40–49 years (A), 50–64 years (B), and greater than 65 years (C), and for all ages by race (D). Scales for DCIS incidence and mammogram utilization on the left and right sides of the graphs, respectively.

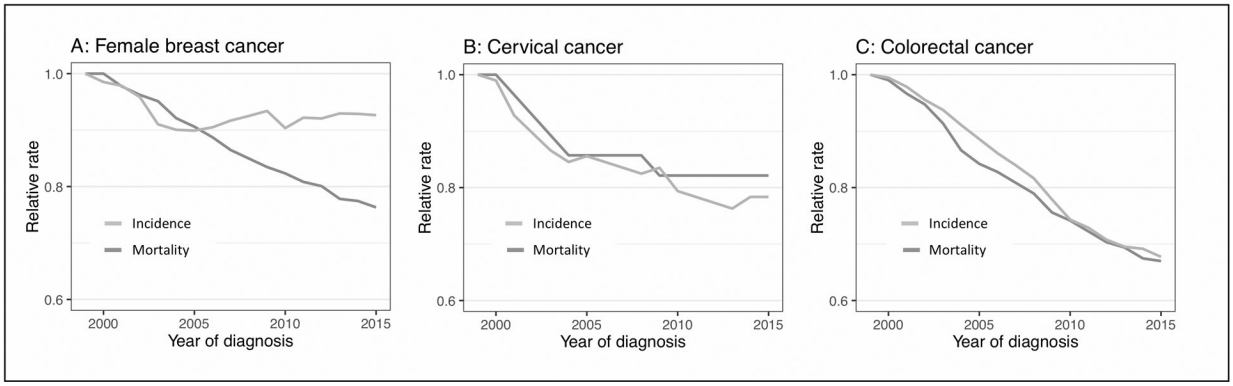

Figure 5: Incidence and mortality rates of female breast, cervical and colorectal (male and female) cancers in the US, 1999–2015

Relative rates are obtained by rescaling the actual rates with respect to the baseline rates in 1999. Data extracted from the U.S. Cancer Statistics Data Visualizations Tool (12).

Table 1:

Trends in patient and tumor features.

	Total (n=145,670)	%	2000–03 (n=34,554)	%	2004–07 (n=37,188)	%	2008–11 (n=41,783)	%	2012–2014 (n=32,145)	%	*p*-value*
Age											<0.001
20–44 years	17,860	12.3	4,503	13	4,725	12.7	4,999	12	3,633	11.3	
45–54 years	40,512	27.8	9,534	27.6	10,710	28.8	11,767	28.2	8,501	26.4	
55–69 years	56,512	38.8	12,510	36.2	13,782	37.1	16,554	39.6	13,666	42.5	
>=70 years	30,786	21.1	8,007	23.2	7,971	21.4	8,463	20.3	6,345	19.7	
Race											<0.001
White	113,396	77.8	28,125	81.4	29,440	79.2	32,084	76.8	23,747	73.9	
Black	15,712	10.8	3,222	9.3	3,897	10.5	4,647	11.1	3,946	12.3	
Other	15,112	10.4	2,978	8.6	3,561	9.5	4,609	11.0	3,964	12.0	
Unknown	1,450	1.0	229	0.7	290	0.8	443	1.1	488	1.5	
ER status											<0.001
Positive	83,168	57.1	4,857	14.1	21,276	57.2	30,865	73.9	26,170	81.4	
Negative	14,592	10.0	1,198	3.5	4,521	12.2	5,125	12.3	3,748	11.7	
Unknown	47,910	32.9	28,499	82.5	11,391	30.6	5,793	13.9	2,227	6.9	
PR status											<0.001
Positive	68,961	47.3	3,909	11.3	17,314	46.6	25,676	61.5	22,062	68.6	
Negative	22,783	15.6	1,731	5	6,732	18.1	8,212	19.7	6,108	19	
Unknown	53,926	37.0	28,914	83.7	13,142	35.3	7,895	18.9	3,975	12.4	
Tumor grade											<0.001
Grade I	17,359	11.9	3,854	11.2	4,282	11.5	5,081	12.2	4,142	12.9	
Grade II	50,862	34.9	10,301	29.8	12,553	33.8	15,450	37	12,558	39.1	
Grade III/IV	55,060	37.8	11,848	34.3	14,803	39.8	16,177	38.7	12,232	38.1	
Unknown	22,389	15.4	8,551	24.7	5,550	14.9	5,075	12.1	3,213	10	
Tumor Size											<0.001
1–10 mm	49,926	34.3	9,865	28.6	12,612	33.9	15,305	36.6	12,144	37.8	
11–30 mm	37,351	25.6	7,510	21.8	9,027	24.3	11,038	26.4	9,776	30.4	
>30 mm	13,162	9.0	2,204	6.4	3,055	8.2	4,156	9.9	3,747	11.7	
Unknown	45,231	31.1	14,891	43.2	12,494	33.6	11,284	27	6,478	20.2	

* Chi-square test

Table 2:

Tumor features in patients diagnosed between 2012–2014.

	n	%
Known tumor grade (n=28,932)		
Grade I	4,142	14.3%
Grade II	12,558	43.4%
Grade III/IV	12,232	42.3%
Known ER status (n=29,918)		
ER-positive	26,170	87.5%
ER-negative	3,748	12.5%
Known PR status (n=28,170)		
PR-positive	22,062	78.3%
PR-negative	6,108	21.7%
Known tumor size (n=25,667)		
1–10 mm	12,144	47.3%
11–30 mm	9,776	38.1%
>30 mm	3,747	14.6%
Known tumor grade, ER and/or PR status * (n=26,552)		
Low risk **	14,762	55.6%
Non-low risk	11,790	44.4%

* Restricted to age>=40 years.

** Grade I/II, ER-positive and/or PR-positive