Comparison of Age-Specific Incidence Rate Patterns for Different Histopathologic Types of Breast Carcinoma

William F. Anderson,[1] Kenneth C. Chu,[2] Shine Chang,[1] and Mark E. Sherman[3]

[1]Division of Cancer Prevention, [2]Center to Reduce Cancer Health Disparities, and [3]Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, NIH, Bethesda, Maryland

Abstract

Objective: The age-specific incidence rate curve for breast carcinoma overall increases rapidly until age 50 years, and then continues to increase at a slower rate for older women. In this analysis, our objective was to compare age-specific incidence rate patterns for different morphologic types of breast carcinoma. Materials and methods: We analyzed age-specific incidence rate curves by histopathologic subclassification using records from 11 standard National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries, diagnosed during the years 1992 to 1999. Data were examined by age <50 and ≥50 years to simulate menopause. Results: Age-specific incidence rate curves showed three dominant patterns: (1) Rates for infiltrating duct carcinoma of no special type (duct NST), tubular, and lobular carcinomas increased rapidly until age 50 years then rose more slowly. (2) Rates for medullary and inflammatory breast carcinomas increased rapidly until age 50 years then failed to increase. (3) Rates for papillary and mucinous carcinomas increased steadily at all ages. Rate patterns varied by estrogen receptor expression but were unaffected by SEER registry, race, nodal status, or grade. Conclusion: Age-specific incidence rates for breast carcinomas differed by histopathologic type. Rates that failed to increase after 50 years suggested that menopause had greater impact on medullary and inflammatory carcinomas than on duct NST, tubular, and lobular carcinomas. Menopause did not seem to have any effect on papillary or mucinous carcinomas as evidenced by steadily rising rates at all ages. Future etiologic and/or prevention studies should consider the impact of age-specific risk factors and/or exposures on different histopathologic types of breast carcinomas. (Cancer Epidemiol Biomarkers Prev 2004; 13(7):1128–35)

Introduction

Armitage and Doll (1, 2) noted a single linear rising trend for the logarithm of non-hormonal epithelial cancer incidence plotted as a function of the logarithm of age-at-diagnosis (e.g., incidence plotted against age produced a straight line on a log-log scale), presumably reflecting accumulated lifetime carcinogenic risks and/or exposures. In contrast, age-specific incidence rate curves for breast carcinoma overall do not demonstrate a simple linear trend on a log-log scale (3, 4). Age-specific incidence rates increase rapidly until age 50 years then increase more slowly for older women, suggesting that some key carcinogenic events occur before rather than after menopause (5, 6).

Furthermore, when rates for sporadic breast carcinoma in the general population are stratified by estrogen receptor (ER) expression, rates for ER-positive and ER-negative (ERP and ERN) diverge into two components (7-9). Rates for ERP increase until age 50 years then increase more slowly, whereas rates for ERN increase until age 50 years then fail to increase. Paradoxically, rates that fail to increase after 50 years suggest that menopause has greater impact on maintaining rates for ERN than for ERP (7-9).

We hypothesized that age-specific incidence rate patterns might also differ for different histopathologic types of breast carcinoma. However, comparison of age-related incidence patterns by morphologic subclassification has been limited (10, 11), and these patterns for histopathologic type defined by ER expression have not been established. We, therefore, analyzed breast carcinoma incidence data for women from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program to define the age-rate patterns for certain morphologic classes and to develop etiologic hypotheses.

Materials and Methods

The SEER program subclassified more than 20 histopathologic types of invasive breast carcinoma, conforming to the International Classification of Diseases for Oncology-2nd edition (ICDO-2; refs. 12, 13). Nearly 75% of all breast carcinoma cases in SEER were infiltrating duct carcinoma of no special type (duct NST), also called duct not otherwise specified (duct NOS; refs. 14, 15). Duct NST was a useful designation that distinguished these tumors from other specific or

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Requests for reprints: William F. Anderson, Division of Cancer Prevention, Department of Health and Human Services, National Cancer Institute, NIH, EPN, Suite 2141, 6130 Executive Boulevard, Bethesda, MD 20892. Phone: (301) 594-7672; Fax: (301) 435-6344. E-mail: wanderso@mail.nih.gov

''special'' types of breast carcinomas, including tubular, lobular, medullary, inflammatory, papillary, and mucinous breast carcinomas (14). Infiltrating duct NST and these other six types of breast carcinoma were the focus of our study.

The SEER program has recorded histopathologic types of breast carcinoma since its inception in 1973, but did not collect ER expression until 1990. In 1992, 2 registries were added to the original 9 SEER sites, for a total of 11 standard SEER registries, including Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, and San Jose-Monterey. Given that this analysis required both histopathologic designation and ER expression, we limited our study to SEER's 11 standard population-based registries collected during the years 1992 to 1999, November 2001 submission (16).

We sequentially filtered the SEER database for the following records:

(1) Women with invasive breast carcinomas (n = 189,634)
(2) Different histopathologic types of breast carcinoma:
  (a) Infiltrating duct carcinoma of no special type (duct NST; n = 139,673; ICDO-2 codes 8010-8011, 8140-8141, 8500)
  (b) Six specific or special types of breast carcinoma (n =29,755)
    (i) Tubular carcinoma (n = 3,474; ICDO-2 codes 8200-8201, 8211)
    (ii) Infiltrating lobular carcinoma (ILC, n = 15,879; ICDO-2 codes 8520-8521)
    (iii) Medullary carcinoma (n = 2,119; ICDO-2 codes 8510-8512)
    (iv) Inflammatory breast carcinoma (IBC, n = 2,108; ICDO-2 code 8530)
    (v) Papillary carcinoma (n = 1,254; ICDO-2 codes 8050, 8260, 8503)
    (vi) Mucinous carcinoma (n = 4,921; ICDO-2 codes 8480-8481)
  (c) Other or unknown types of breast carcinoma (n = 20,206)

Patient age-at-diagnosis, tumor size-at-diagnosis, race, and ER expression were arranged to compare given characteristics by morphologic class. Data were examined by age <50 years and ≥50 years to simulate rate changes occurring before and after menopause. Because no centralized laboratory was used to determine hormone receptor expression, each SEER registry coded ER expression as positive (ERP), negative (ERN), missing, borderline, or unknown. We combined missing, borderline, or unknown data into one group, designated as ''Unknown.''

Incidence rate data with SE were obtained from SEER stat 4.2 (16). All rates were expressed per 100,000 person-years to the nearest 0.001 decimal point and age-adjusted by the direct method to the 2000 United States standard population (17). As originally described by Armitage and Doll, the logarithm of rates was plotted as a function of the logarithm of age-at-diagnosis (1, 2). We fitted these log-log age-specific rate curves with Poisson regression analyses to quantify slope changes and to assess random variation, as previously discussed (7, 8). Briefly, log-log age-specific rates were evaluated at the midpoint of 5-year age groups with the focus of our inference on the slopes before and after the change-point.

Results

Descriptive Statistics. The top portion of Table 1 presents frequency, percentage of total cases, percentage range of total cases for white race in those SEER registries comprising at least 90% of all breast carcinoma cases, percentage range expected from other published sources (15, 18, 19), mean and median age-at-diagnosis, mean tumor size-at-diagnosis, and incidence rate by histopathologic types. Duct NST (n = 139,673, 73.7%) and ILC (n = 15,879, 8.4%) comprised the majority of all breast carcinoma cases with most of the balance consisting of ''special-types'' of breast carcinoma, that is, tubular, medullary, inflammatory, papillary, and mucinous breast carcinomas. Other or unknown histopathologic types (n = 20,206) were beyond the scope of this project.

Median ages-at-diagnosis by histopathologic types were 62 years for all cases combined, 62 years for duct NST, 64 years for tubular, 66 years for ILC, 51 years for medullary, 56 years for IBC, 70 years for papillary, and 71 years for mucinous breast carcinoma. Mean tumor sizes-at-diagnosis ranged from 1.1 to 2.5 cm for histopathologic subclassifications except for IBC, which had a mean size of 5.9 cm.

Sample size (N), incidence rates with SE for the different histopathologic types of breast carcinoma. Patient demographics and ER expression for each morphologic subtype were arranged to express relative risk for a given characteristic as incidence rate ratio (RR), in which the rate for a given characteristic was compared with a referent rate with an assigned RR of 1.0. RR for decile age groups relative to age <50 years were greatest between ages 70 and 79 years for duct NST (RR = 10.4), tubular carcinoma (RR = 16.2), and ILC (20.3). RR for decile age groups peaked at earlier ages for medullary carcinoma and IBC, and at later ages for papillary and mucinous breast carcinomas. For example, RR was 3.9 and 5.6 between ages 50 and 59 for medullary carcinoma and IBC compared with 32.2 and 32.1 at ages >80 years for papillary and mucinous breast carcinomas.

There were 159,108 white, 15,886 black, and 13,296 women from other races for all breast carcinoma cases combined. RR for black relative to white race was greatest for medullary carcinoma, IBC, and papillary carcinoma, that is, 2.0 for medullary carcinoma, 1.4 for IBC, and 1.8 for papillary carcinoma. ERN compared with ERP was most predictive for medullary carcinoma (RR = 3.5).

Age-Specific Incidence Rate Curves for Histopathologic Class by ER Expression. Log-log age-specific incidence rate curves for all cases combined and each histopathologic class were stratified by ERP and ERN in Fig. 1. We fitted these log-log age-rate curves with regression analysis to quantify the age of slope change (i.e., age of change-point, Table 2). All slope changes before and after the change-point were highly statistically significant ($P < 0.001$). Absolute P values presented in Table 2

Table 1. Descriptive statistics by histopathologic subtypes in SEER's 12 registry database among female breast carcinoma cases collected during 1992 to 1999

Variable	All cases combined				Duct NST				Tubular				Lobular (ILC)			
Frequency (*N*)	189,634				139,673				3,474				15,879			
% of total cases	100.0%				73.7%				1.8%				8.4%			
% SEER (average)	100.0%				67.5%-77.3% (73.1%)				1.3%-3.4% (2.0%)				7.8%-10.1% (9.0%)			
% Expected	100.0%				65.0%-80.0%				<2.0%				<10.0%			
Mean age (SE)	61.9 (0.03)				61.5 (0.04)				63.0 (0.22)				65.1 (0.11)			
Median age	62.0				62.0				64.0				66.0			
Mean size (SE)	2.17 (0.05)				2.13 (0.06)				1.1 (0.16)				2.5 (0.19)			
Rate (SE)	132.1 (0.3)				97.4 (0.26)				2.4 (0.04)				11 (0.09)			
Variable	*N*	Rate	SE	RR	*N*	Rate	SE	RR	*N*	Rate	SE	RR	*N*	Rate	SE	RR
Patient demographics																
Age																
<50	44,543	42.4	0.20	1.0	34,120	32.4	0.18	1.0	605	0.6	0.02	1.0	2,417	2.3	0.05	1.0
50-59	39,254	284.3	1.44	6.7	29,220	211.6	1.24	6.5	806	5.8	0.21	9.9	3,084	22.3	0.40	9.5
60-69	40,965	380.6	1.88	9.0	30,018	279.1	1.61	8.6	874	8.1	0.28	13.7	3,815	35.3	0.57	15.1
70-79	41,411	468.6	2.30	11.0	29,785	337.0	1.95	10.4	847	9.6	0.33	16.2	4,207	47.6	0.73	20.3
80+	23,461	432.0	2.82	10.2	16,530	304.6	2.37	9.4	342	6.4	0.34	10.8	2,356	43.4	0.90	18.5
Race																
White	159,108	137.0	0.35	1.0	116,322	100.3	0.30	1.0	3,148	2.7	0.05	1.0	14,315	12.2	0.10	1.0
Black	15,886	120.7	0.97	0.9	11,931	90.2	0.84	0.9	146	1.1	0.10	0.4	875	6.9	0.24	0.6
Other	13,296				10,427				154				584			
Unknown	1,344				993				26				105			
Estrogen Receptor (ER)																
ERP	111,215	77.5	0.23	1.0	81,621	56.9	0.20	1.0	2,299	1.6	0.03	1.0	11,389	7.9	0.07	1.0
ERN	34,429	24.2	0.13	0.3	27,528	19.4	0.12	0.3	219	0.2	0.01	0.1	1,239	0.9	0.02	0.1
Unknown	43,990				30,524				956				3,251			

Variable	Medullary				Inflammatory (IBC)				Papillary				Mucinous			
Frequency (*N*)	2,119				2,108				1,254				4,921			
% of total cases	1.1%				1.1%				0.7%				2.6%			
% SEER (average)	0.7%-1.5% (1.0%)				0.5%-1.9% (1.1%)				0.4%-0.9% (0.6%)				2.1%-3.0% (2.6%)			
% Expected	<5.0%				1.0%-3.0%				1.0%-2.0%				2.0%			
Mean age (SE)	53 (0.30)				57.7 (0.32)				67.8 (0.39)				68.3 (0.20)			
Median age	51.0				56.0				70.0				71.0			
Mean size (SE)	2.5 (0.58)				5.9 (2.29)				2.0 (0.67)				2.0 (0.29)			
Rate (SE)	1.5 (0.03)				1.5 (0.03)				0.9 (0.02)				3.3 (0.05)			
Variable	*N*	Rate	SE	RR	*N*	Rate	SE	RR	*N*	Rate	SE	RR	*N*	Rate	SE	RR
Patient demographics																
Age																
<50	982	0.9	0.03	1.0	707	0.7	0.03	1.0	163	0.2	0.01	1.0	639	0.6	0.02	1.0
50-59	499	3.6	0.16	3.9	512	3.7	0.16	5.6	159	1.1	0.09	7.4	606	4.4	0.18	7.2
60-69	331	3.1	0.17	3.4	374	3.5	0.18	5.2	277	2.6	0.16	16.6	1,048	9.6	0.30	15.8
70-79	224	2.5	0.17	2.8	328	3.7	0.20	5.6	384	4.3	0.22	28.0	1,564	17.7	0.45	29.1
80+	83	1.5	0.17	1.7	187	3.4	0.25	5.2	271	5.0	0.30	32.2	1,064	19.6	0.60	32.1
Race																
White	1,567	1.4	0.04	1.0	1,710	1.5	0.04	1.0	947	0.8	0.03	1.0	4,077	3.3	0.05	1.0
Black	385	2.7	0.14	2.0	274	2.0	0.12	1.4	171	1.4	0.11	1.8	373	3.1	0.16	0.9
Other	160				118				130				435			
Unknown	7				6				6				36			
Estrogen Receptor (ER)																
ERP	372	0.3	0.01	1.0	723	0.5	0.02	1.0	738	0.5	0.02	1.0	3,518	2.4	0.04	1.0
ERN	1,302	0.9	0.03	3.5	667	0.5	0.02	0.9	114	0.1	0.01	0.2	222	0.2	0.01	0.1
Unknown	445				718				402				1,181			

Abbreviations: % SEER, range for percentage of total cases for white subjects in those SEER registries comprising at least 90% of all breast carcinoma cases; % Expected, expected percentage range for each morphologic type as documented from other published studies; Mean and median age, mean and median age-at-diagnosis in years; Mean size, mean tumor size-at-diagnosis in centimeters; Rate, age-adjusted (2000 US standard) incidence rate expressed per 100,000 person-years; RR, rate ratio where a given characteristic is compared to a reference variable with an assigned value of 1.0.

compared the slope of the age-rate curve after the change-point to a horizontal or flat line with a slope of zero, in which $P > 0.05$ suggested no difference from a flat or horizontal line.

We observed three dominant age-rate patterns in Fig. 1, although definite conclusions for some subsets are not possible due to small sample sizes; for example, ERN for tubular ($n = 219$), ERP for medullary ($n = 372$), ERN for papillary ($n = 114$), and ERN for mucinous carcinomas ($n = 222$). A vertical reference line at age 50 years represented our surrogate cut-point for menopause.

For the first rate pattern, total rates for all cases combined, duct NST, tubular carcinoma, and ILC increased sharply until age 50 years then rose more slowly (Fig. 1A-D). Rates diverged for these morphologic types defined by ER expression; that is, rates for ERP carcinomas increased sharply until approximately age 50 years then rose more slowly for older women, whereas rates for ERN increased until age 50 years then flattened. Table 2 confirmed a slower rate of increase after the change-point for total and ERP tumors among all cases combined, duct NST, tubular, and lobular breast carcinomas, whereas the slopes for these morphologic types defined by ERN expression approached zero after the change-point. Indeed, ERN slopes after the change-point were actually no different than zero ($P > 0.05$, Table 2) for all cases combined, duct NST, and tubular carcinoma. The 'slope after change' for ILC defined by ERN was greater than zero (i.e., 1.3 with $P < 0.001$, Table 2), but still was closer to zero than the slope after change for ILC overall and ERP tumors (i.e., 1.3 compared with 2.6, respectively). The change-point for most histopathologic types occurred at or near age 52 years.

For the second rate pattern, total rates for medullary carcinoma and IBC increased until 50 years then failed to increase irrespective of ER expression (Fig. 1E and F and Table 2). Notably, total rates declined after 50 years for medullary carcinoma, with a negative slope of -0.7. On the other hand, total rates flattened after 50 years for IBC with a positive slope of 0.4 that was not different than a horizontal line ($P = 0.0469$).

For the third rate pattern, rates for papillary and mucinous carcinomas increased steadily at all ages

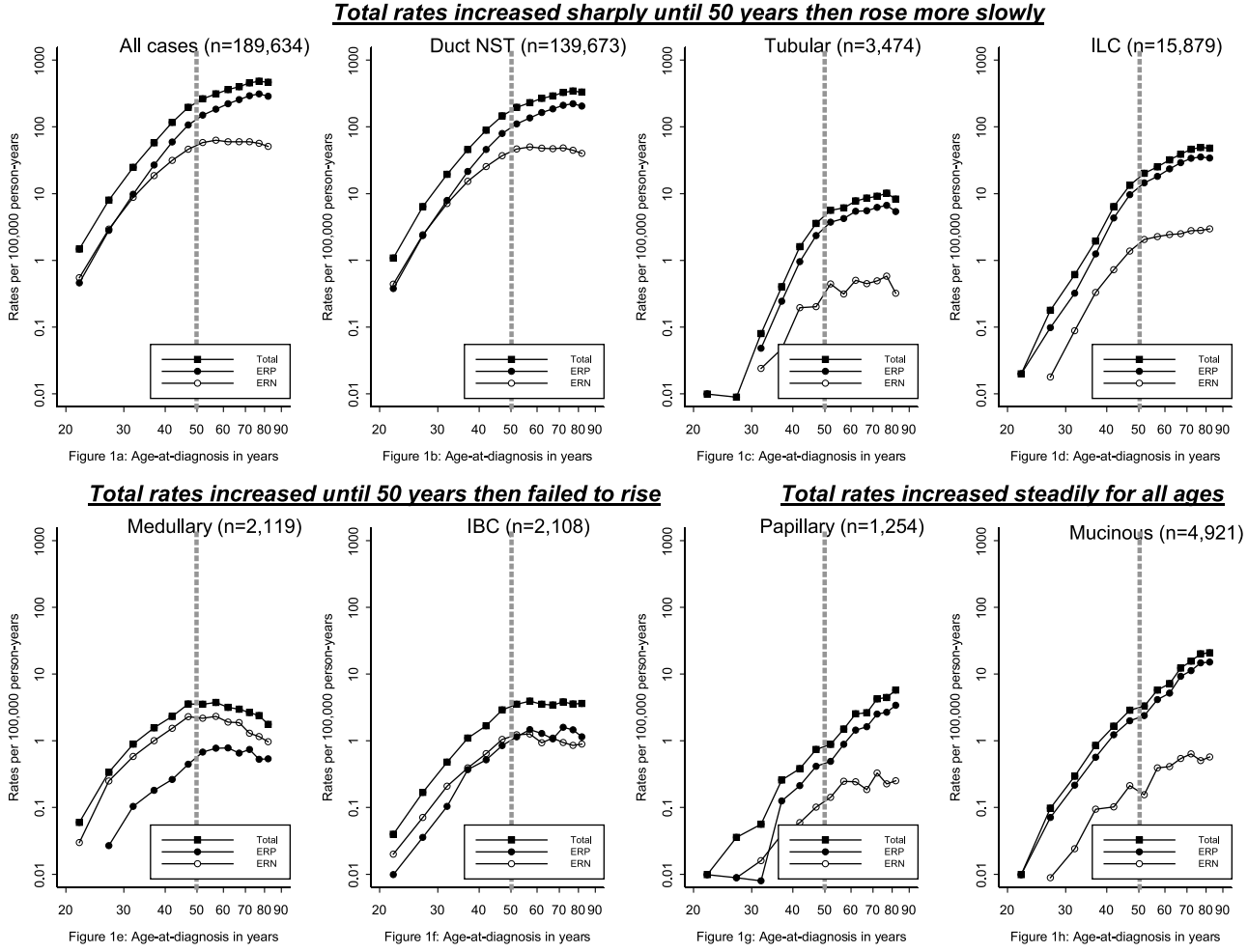

Figure 1. Age-specific incidence rates for all cases combined and each histopathologic type, stratified by ERP and ERN expression. Abbreviations: NST, infiltrating ductal carcinoma no special type; ILC, infiltrating lobular carcinoma; and IBC, inflammatory breast carcinoma.

Table 2. The fits for log-log age-specific rate regression models with one change-point to the SEER incidence rates for each histopathologic subtype

Histopathologic type	Age of change-point*	Slope before change	Slope after change	*P* value†
All cases combined				
Total	52	5.7	1.8	<0.0001
ERP	52	6.4	2.1	<0.0001
ERN	52	4.9	0.3	0.1077
Duct NST				
Total	52	5.6	1.7	<0.0001
ERP	52	6.2	2.0	<0.0001
ERN	52	4.8	0.3	0.1607
Tubular				
Total	52	8.4	1.7	<0.0001
ERP	52	8.8	1.8	<0.0001
ERN	57	4.6	0.7	0.2077
Lobular (ILC)				
Total	52	8.2	2.6	<0.0001
ERP	52	8.8	2.6	<0.0001
ERN	52	7.2	1.3	<0.0001
Medullary				
Total	52	4.0	−0.7	<0.0001
ERP	57	4.4	−0.3	0.4157
ERN	52	3.9	−1.1	<0.0001
Inflammatory (IBC)				
Total	52	5.1	0.4	0.0469
ERP	52	5.4	0.9	0.0081
ERN	52	4.8	−0.4	0.0805
Papillary				
Total	NC	3.8	NA	NA
ERP	NC	4.0	NA	NA
ERN	62	3.9	0.4	0.5152
Mucinous				
Total	NC	4.4	NA	NA
ERP	NC	4.5	NA	NA
ERN	NC	3.1	NA	NA

*All slope changes before and after the change-point are statistically significant (P value < 0.001).
†The P values are for comparison of the slope after the change-point with zero; NC, no change; NA, not applicable.

irrespective of ER expression, with one exception (Fig. 1G and H and Table 2). At age 62 years, the slope after change for papillary ERN tumors decreased to 0.4, approaching a horizontal line (P = 0.5152). Rates for unknown ER expression approximated rates for total and ERP breast carcinomas among all histopathologic types (data not shown).

Age-Specific Incidence Rates for Histopathologic Class by Black and White Race. Log-log incidence rates were stratified by race in Fig. 2. Rates for duct NST and ILC were higher among black than white women until approximately age 40 years, and then rates were higher for older white women. Rates for medullary, IBC, and papillary carcinomas were higher among black women for all ages. In contrast, rates for tubular and mucinous carcinomas were higher among white women for all ages. Although age-specific rates differed by race, the overall shape of the age-specific incidence curves were similar for black and white women for each histopathologic subclassification, that is, both black and white women displayed the same three dominant rate patterns for each histopathologic class.

The percentage of histopathologic subtypes for white subjects varied by SEER geographic location, as documented in Table 1 (% SEER). Determination of percentage range was limited to white subjects to examine geographic variation within SEER beyond racial differences. For example, % SEER for duct NST varied from 67.5% to 77.3% with an average of 73.1%. Similar variations were noted for all morphologic subclasses. However, for each morphologic class, the average % SEER was very similar to percentage of total cases for the SEER database overall. The percentage of total cases for the SEER database was also within the expected percentage range for each morphologic type as documented from other published resources (15, 18, 19); see percentage expected in Table 1. Moreover, age-specific rate patterns for each histopathologic type among those SEER registries with the lowest and highest percentage ranges were nearly identical to the composite rate curves (data not shown). Age-specific rate patterns by histopathologic class were also unaffected by axillary lymph nodal status and nuclear grade.

Discussion

Our analysis of SEER incidence data for nearly 200,000 invasive breast carcinoma cases diagnosed during 1992 to 1999 identified three distinctive incidence rate patterns, closely associated with age-at-diagnosis, histopathologic type, and ER expression irrespective of SEER registry, black or white race, lymph nodal status, or nuclear grade. First, there was an age-specific incidence rate curve that increased rapidly until menopause then rose more slowly with advancing age, characteristic of ERP for all breast carcinomas cases combined. Second, there was a rate curve that increased rapidly until menopause then failed to increase, characteristic of ERN for all breast carcinomas cases combined. Third, there was a rate curve that increased steadily at all ages, similar to non-hormonal epithelial tumors, such as colorectal carcinoma (1, 2, 20). Possible causes for these different age-specific incidence rate patterns are complex, including histopathologic or receptor misclassification, cohort or screening artifacts, and/or diverse etiologies. On the other hand, similar age-specific incidence rate patterns possibly reflected similar etiologies.

For example, incidence rate patterns for all breast carcinoma cases combined were similar to duct NST (Fig. 1A and B), which was not surprising given that most breast carcinomas were duct NST (i.e., 74%). Total and ERP rates for tubular carcinoma resembled total and ERP rates for duct NST (Fig. 1B and C), which also might be predicted given that tubular carcinoma reflected the archetypical well-differentiated duct NST (14, 15). Rates for the smaller subset of ERN tubular carcinomas (n = 219) also resembled ERN rates for duct NST. However, it is unclear if these ERN tubular carcinomas represented misclassification of histopathologic type and/or ER expression or the existence of a minor class of breast carcinomas with distinctive biological features.

Tubular and lobular carcinomas have traditionally been regarded as distinct histopathologic types. However, the identification of mixed tumors that appear as a composite of tubular and lobular components, suggests that tubular and lobular breast carcinomas may be related types derived from the common terminal

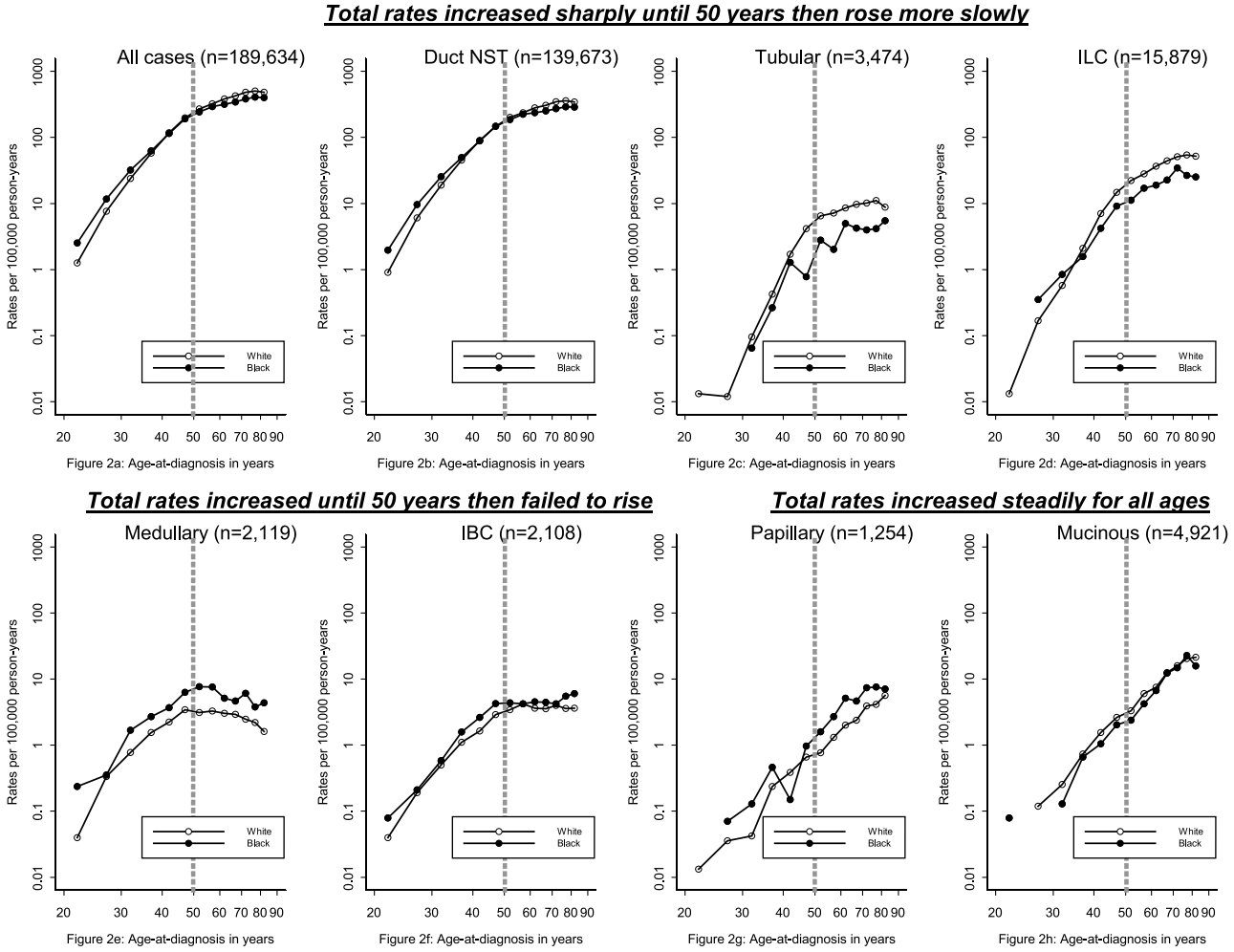

Figure 2. Age-specific incidence rates for all cases combined and each histopathologic type, stratified by black and white race. Abbreviations: NST, infiltrating ductal carcinoma no special type; ILC, infiltrating lobular carcinoma; and IBC, inflammatory breast carcinoma.

duct-lobular unit or TDLU (21), a hypothesis supported by their similar incidence rate patterns (Fig. 1C and D). A growing body of epidemiologic evidence linking postmenopausal lobular (22-25) and possibly tubular (25) breast carcinomas to use of hormone replacement therapy is also consistent with their similar age-specific risks or incidence rate curves. Albeit, all studies have not found increased breast cancer risk for hormone replacement therapy by histopathologic type (26, 27).

Incidence rates on the whole for medullary carcinomas and IBC were like ERN rates for all breast carcinoma cases (Fig. 1A, E, and F), irrespective of their own ER expression. Both medullary and inflammatory breast carcinomas are generally composed of poorly differentiated tumor cells with low ER content. Approximately 78% of medullary carcinomas were ERN, whereas nearly half of IBC were ERN. Flat postmenopausal rates for both ERP and ERN were first described for IBC (28, 29), but have not been described for medullary carcinomas. Rates for medullary carcinoma may actually decline among women older than age 50 years; however, the certainty of this observation is limited by small numbers and by the lack of rigorous pathologic review in this analysis.

Further research is required to ascertain whether genetic predisposition and/or early life exposures contributed to the findings for medullary and inflammatory breast carcinomas. Medullary carcinomas and ''atypical'' medullary carcinomas have been associated with hereditary mutations in the *BRCA1* gene (30-32), so at least a fraction of these tumors can be considered to represent the development of cancer at a young age among women with a strong genetic risk. Primary inflammatory carcinomas have been associated with early age-at-onset and bilaterality (33, 34), features consistent with familial breast carcinoma (35).

Incidence rates for papillary and mucinous carcinomas generally rose with age irrespective of their ER expression (Fig. 1G and H), suggesting that these breast carcinomas reflected the effects of cumulative genetic damage resulting from lifetime deleterious exposures. This rate pattern was unlike all other breast carcinomas but similar to most non-hormonal epithelial organ

systems (1, 2, 20). It is noteworthy that the pathogenesis of these generally well-differentiated tumors is unusual. Many papillary carcinomas arise from large epithelial ducts proximal to the common terminal duct-lobular unit. These large ducts are present in both sexes, may be relatively unresponsive to female reproductive hormones, and tend to persist with increasing age (11). Menopause did not seem to have any effect on papillary carcinomas as evidenced by steadily rising rates at all ages. A similar rate pattern for mucinous carcinoma suggested that it too was unaffected by menopause.

Our data confirmed that rates for breast carcinoma overall were higher for black than for white women until age 40 years; and then there was ethnic cross-over, resulting in higher rates for whites than for blacks (36, 37). However, this ethnic cross-over for black and white race was only found among NST and ILC, and not for other histopathologic types. For tubular and mucinous carcinomas, rates were higher for whites than for blacks at all ages. For medullary carcinoma, IBC, and papillary carcinomas, rates were generally higher for blacks than for whites at all ages. Despite racial differences for different histopathologic types, the shapes of the age-specific rate curves for a given histopathologic type were nearly identical for both races. This suggests that the etiologic factors related to these tumors act similarly, irrespective of race.

The main strength of our study was the large-scale population-based design. Potential weaknesses included (1) absent histopathologic slide review, (2) incomplete and non-standardized data for ER expression, and (3) lack of data on menopausal status and other factors, such as method of detection, which could impact results. The lack of central pathologic slide review is a concern in a population-based analysis of morphologic class. Although there was some geographic variation in rates that could not be entirely accounted for by difference in racial distributions, the average percentage range for each morphologic class was very similar to the percentage of total cases for the SEER database overall (Table 1). It was also reassuring that the percentage distribution for different histopathologic types was similar to other published results. Moreover, the age-specific rate patterns for each morphologic class among registries with the lowest and highest percentage ranges were virtually identical to the composite rate curves, implying similar biology. Theoretically, the large-scale population-based design of this study should also balance diagnostic variation among different pathologists and geographic SEER regions, reflecting 'real' world practice patterns within the United States. Although assays for ER status were not standardized and data were missing for a substantial percentage of cases, there was no evidence that this had an important impact on the data. In particular, rate patterns for cases with unknown ER status resembled those for breast cancers as a whole. Finally, we used an age of 50 years as a surrogate for menopausal status, which has been shown to provide a reasonable analytic practice (38).

In conclusion, it is intriguing to consider the age-specific relationship between histogenesis, ER expression, and carcinogenesis. It is well established that early age-at-onset is associated with undifferentiated tumor types and low ER content (10, 39, 40). Thus, poorly differentiated medullary and inflammatory breast carcinomas with relatively low ERP expression developed at rather early ages, whereas well-differentiated papillary and mucinous tumors with high ERP levels were more common in elderly women. Duct NST with intermediate ERP content arose in middle-aged or older women. The clear divergence of age-specific rate patterns by ER expression for some but not for all breast carcinomas is a curious phenomenon, which is not easily reconciled with a simple linear model of breast carcinogenesis—as previously suggested (9, 28, 41). Further analytic studies are clearly needed to systematically assess whether it is histopathologic or hormone receptor phenotype that more accurately reflects etiologic mechanisms. Addressing this question comprehensively will require large studies that include collection and testing of biological specimens, including breast tissue. This effort is warranted because refining our etiologic understanding of breast carcinoma may have important implications for risk assessment, prevention, and treatment.

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