Breast Cancer Res Treat (2006) 99:333–340
DOI 10.1007/s10549-006-9214-z

EPIDEMIOLOGY

Assessing the impact of screening mammography: breast cancer incidence and mortality rates in Connecticut (1943–2002)

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Received: 22 February 2006 / Accepted: 2 March 2006 / Published online: 9 May 2006

Abstract
Background Randomized controlled studies demonstrate that early detection and intervention reduce breast cancer mortality by approximately 25%. Though the ultimate goal of screening is to reduce breast cancer deaths, the immediate goal is to detect and treat early-stage tumors before they pose a threat to life.
Materials and methods To assess the impact of early detection and intervention in the general population, we analyzed breast cancer incidence and mortality rates in the NCI's Historical Connecticut Tumor Registry (1943–2002).
Results Though breast cancer rates increased for the entire study period, overall incidence rates rose faster than previously following the initiation of mammography screening in the early 1980s in the United States. Of note, stage-specific incidence rates increased 152% (53.2–133.9 per 100,000 woman-years) for early-stage tumors and fell 16% (56.1–47.2 per 100,000 woman-years) for late-stage breast cancers. Period- and cohort-age-specific incidence rates rose dramatically for early-stage tumors among women targeted for screening (ages 40–80 years), whereas rates for regional and distant stages declined modestly among women ages >50 years. Breast cancer mortality rates fell 31.6%.
Conclusions Along with increases in incidence rates for early-stage tumors, rates for late-stage disease and breast cancer mortality declined following widespread screening mammography, consistent with effective early detection and improved treatment over time. However, the disparity between the dramatic rise in early-stage tumors compared to the more modest declines in late-stage disease and mortality suggests that many mammography-derived early-stage lesions may never progress to late-stage cancers and pose a threat to life.

Keywords Lead time bias · Length bias · Prognostic factors · Calendar-period effects · Birth cohort effects · Breast cancer incidence · Breast cancer mortality

This research was supported in part by the Intramural Research Program of the NIH/National Cancer Institute. The authors would like to thank John Lahey of IMS, Inc. for figure preparation.

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Introduction

Randomized controlled trials confirm that mammography screening reduces breast cancer mortality by approximately 25% [1, 2], and the recent declines in United States breast cancer mortality rates have been attributed to screening along with improved treatment [3]. Indeed, population-based mathematical models suggest that approximately one-half of the total reduction in breast cancer death rates

is due to screening with adjuvant treatment contributing the rest [4].

Notwithstanding the acknowledged mortality benefits for early detection and intervention, randomized controlled studies and mathematical models do not assess the potential risk of diagnosing (and treating) biologically indolent early-stage breast tumors, which pose little or no threat to life [5–8]. We speculated that an ideal program of mass screening would detect only those early-stage tumors destined to progress to late-stage disease, yielding population increases in early-stage lesions with reciprocal declines in late-stage disease and breast cancer mortality over time.

Though the method of initial breast cancer diagnosis and complete treatment records are not available in large-scale population-based datasets such as the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), calendar-period trends can serve as surrogate measures for the net impact of medical interventions over time [9]. The SEER program did not begin until 1973 and all of SEER's original 9 tumor registries were not included in the program until 1975. Therefore, to analyze long-term breast cancer trends, before and after widespread screening mammography, we used the NCI's Connecticut Historical Cancer Database (1943–2002) [10].

Material and methods

To create one continuous dataset with 60 years of incidence data from 1943 to 2002, we combined breast cancer records from the NCI's Connecticut Historical Cancer Database for the years 1943–1972 with breast cancer cases from SEER's Connecticut Tumor Registry Database for the years 1973–2002. Breast cancer mortality data were available from the National Center for Health Statistics (NCHS, www.cdc.gov.nchs) for the years 1953–2002.

Tumor characteristics

Data on standard demographics and tumor characteristics were dichotomized into favorable (low-risk) and unfavorable (high-risk) groups. Tumor size was categorized as ≤2.0 cm (low-risk) versus >2.0 cm (high-risk), lymph node status was negative (low-risk) versus positive (high-risk), estrogen receptor (ER) expression were categorized separately as positive (low-risk) or negative (high-risk). SEER designated malignant behavior as *in-situ* versus invasive breast cancer. SEER's historical staging system defined invasive localized disease as limited to the breast, invasive regional disease as limited to near-by lymph nodes or other organs, and invasive distant disease as systemic metastases.

Calendar-period of diagnosis, age at diagnosis, and birth cohort

The study period 1943–2002 was divided into twelve 5-year calendar-periods of diagnosis (1943–1947 to 1998–2002) and six 10-year calendar-periods of diagnosis (1943–1952 to 1993–2002). There also were twelve 5-year age group intervals at diagnosis (25–29 to 80–84 years) and six 10-year age group intervals (25–34 to 75–84 years).

Given the relationship (birth cohort)=(year of diagnosis) minus (age at diagnosis), we used the twelve 5-year calendar-periods and the twelve 5-year groups intervals to create twelve 10-year birth-cohorts, referred to by the mid-year of birth (circa 1863–1973). For example, the 1st or oldest cohort mid-year of birth 1863 *equaled* 1945.5 (mid-year of the calendar-period 1943–1947) *minus* 82.5 years (mid-year of the age group interval 80–84 years). The last or youngest cohort mid-year of birth 1973 *equaled* 2000.5 (mid-year of the calendar-period 1998–2002) *minus* 27.5 years (mid-year of the age group interval 25–29 years).

Thus, our dataset captured newly diagnosed breast cancer cases among women of all ages before and after widespread screening mammography. For example, women born in 1863 were ages 80–84 years at diagnosis during the earliest calendar-period 1943–1947, and therefore, developed breast cancer decades prior to routine screening mammography. Women born in 1973 were ages 25–29 years during the latest calendar-period 1998–2002, and thus, were too young for routine screening mammography.

Statistical methods

Age-specific and age-adjusted (2000 U.S. standard) incidence and mortality rates per 100,000 woman-years were calculated with SEER*Stat 6.1.4. SEER's Joinpoint regression program was used to identify changes in secular trend [11]. In brief, Joinpoint is a public-use statistical software for the analyses of trends to determine whether apparent changes in trend data are statistically significant. The software takes the annual rate data and fits the simplest Joinpoint (knots or nodes) that the data will allow. The user can choose the number of Joinpoints as well as the significance level.

Results

The Connecticut Tumor Registry has collected data on cancer cases diagnosed among residents of the state of Connecticut since 1935. Trends were plotted graphically such that a slope of 10° portrayed a rate of change of 1% per year [12]. There were n=107,840 breast cases

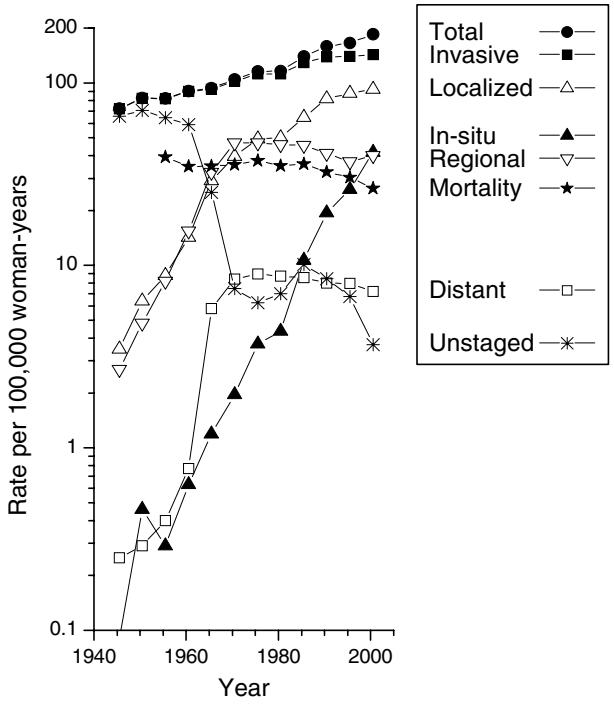

Fig. 1 Female breast cancer mortality and incidence trends in Connecticut by stage and twelve 5-year time periods of diagnosis (1943–1947 to 1998–2002). Note: 'Total' includes *in-situ* and invasive breast cancers

diagnosed during the years 1943–2002, for an even 60 years of data. Incidence and mortality trends are shown in Fig. 1. Using SEER's Joinpoint Regression program, the year 1979 was a point of change where total breast cancer incidence rates began to increase faster than previously. Incidence rates for *in-situ* and invasive tumors increased continuously during the study period, albeit considerably more rapidly for *in-situ* than for invasive breast cancers. During the 1960s and early 1970s, incidence rates for unknown stage fell while rates for localized and regional disease rose in tandem. Coinciding with the 1979 point of change, rates increased for localized and declined for regional and distant stages. Breast cancer mortality rates peaked at 38 per 100,000 woman years during 1973–1977 then dropped to 26 per 100,000 woman years during 1998–2002, for a decline of 31.6%.

After widespread screening mammography, the largest percentage change (%CH) in age-specific incidence rates occurred among ages 50–59 years (71%), 60–69 years (82%), 70–79 years (74%) (Table 1). *In-situ* breast cancers rose steadily from 3.7 to 41.6 per 100,000 woman-years (1024%). During the same time period, rates increased 86% for localized stage but declined for regional (15%) and distant stages (20%). For early-stage tumors combined (*in-situ*+localized), incidence rates increased 152% from 53.2 per 100,000 woman-years in 1973–1977 to 133.9 per 100,000 woman-years in 1998–2002. Early-stage tumors now account for 73% of all newly diagnosed breast cancer cases. For late-stage lesions combined (regional+distant), incidence rates fell 16% during this same time period.

SEER did not record tumor size, axillary lymph nodal status, and histologic grade until 1988, and did not collect hormone receptor expression until 1990. From 1988–1992 to 1998–2002, rates for tumors ≤2.0 cm and negative axillary nodes increased 29% and 42%, respectively, whereas rates for tumors >2.0 cm and positive nodes were relatively stable. From 1993–1997 to 1998–2002, rates for estrogen positive breast cancers rose 21% while rates for estrogen negative tumors declined slightly.

Figure 2 shows age-specific incidence rates (Fig. 2a) and mortality rates (Fig. 2b) by calendar year and cohort mid-year of birth. By the early 1980s, age-specific rates by calendar year began to increase faster than previously among all age-groups, except for the youngest groups (Fig. 2a). Age-specific rates by cohort year of birth also rose for all birth cohorts after 1880, except for the very youngest. The increases were less consistent prior to the 1979 year of diagnosis and before the 1900 year of birth. Beginning in the 1980s to 1990s, age-specific mortality rates decreased among all age-groups, except for the oldest group (Fig. 2b). Similarly, age-specific rates decreased for most birth cohorts, though the patterns varied among the oldest women, born prior to the 1900s.

Figure 3a shows period-age-specific incidence rates for six 10-year calendar-periods of diagnosis. Age-specific rates for total cases (*in-situ*+invasive) and invasive breast cancers rose rapidly until age 50 years, and then continued to rise more slowly among older women. Rates increased for all succeeding time periods (beginning with 1943–1952 and ending with 1993–2002), especially among women targeted for screening, ages 40–80 years.

Given the lack of good data for stage prior to the 1970s, period-age-specific rates were not calculated by stage before the 1973–1982 decade, effectively eliminating consideration of stage-specific rates during the earliest time periods, i.e., 1943–1952, 1953–1962, and 1963–1972. For each of the remaining three time periods (Fig. 3a), age-specific rates *increased* with each succeeding decade of diagnosis for *in-situ* and localized stages (beginning with 1973–1982 and ending with 1993–2002), though considerably more for *in-situ* than localized breast cancers. In contrast, age-specific rates *decreased* modestly with each succeeding decade for regional and distant stages, though more for regional than distant tumors. Cross-sectional rates for *in-situ* lesions fell noticeably during each time interval after age 70 years, as previously reported [13].

Figure 3b shows cohort-age-specific incidence rates for nine cohort mid-years of birth (circa 1878–1958). Age-specific rates for total cases (*in-situ*+invasive) and invasive

Table 1 Female breast cancer incidence in Connecticut, 1973–1977 to 1998–2002

Time period	1973–1977			1978–1982			1983–1987			1988–1992			1993–1997			1998–2002			%CH 1973–1977 to 1998–2002
Variable	*N*	Rate	SE	*N*	Rate	SE	*N*	Rate	SE	*N*	Rate	SE	*N*	Rate	SE	*N*	Rate	SE	
Total cases	8,741	115.5	1.3	9,451	116.2	1.2	12,082	139.7	1.3	14,378	158.8	1.3	15,582	165.6	1.3	18,364	184.8	1.4	60%
Age																			
<30	62	1.6	0.2	66	1.6	0.2	81	1.8	0.2	73	1.7	0.2	67	1.8	0.2	46	1.4	0.2	−10%
30–39	436	47.8	2.3	549	50.3	2.2	717	57.2	2.1	740	55.1	2.0	765	53.6	1.9	855	62.1	2.3	30%
40–49	1,537	167.2	4.3	1,296	150.9	4.2	1,695	178.6	4.3	2,291	202.5	4.2	2,726	216.0	4.1	3,262	234.1	4.1	40%
50–59	2,255	239.5	5.1	2,094	225.4	5.0	2,333	273.9	5.8	2,507	316.3	6.3	3,054	350.7	6.3	4,336	410.6	4.7	71%
60–69	1,990	290.2	6.5	2,443	318.4	6.4	3,147	389.4	6.9	3,580	460.3	7.7	3,332	473.1	8.2	3,538	527.5	6.5	82%
70–79	1,566	361.7	9.2	1,873	385.1	8.9	2,629	477.4	9.3	3,296	545.6	9.5	3,563	563.4	9.4	3,882	630.6	8.8	74%
80+	895	382.7	12.9	1,130	410.1	12.2	1,480	472.6	12.3	1,891	530.5	12.2	2,075	502.3	11.0	2,445	525.8	14.6	37%
SEER stage																			
In-situ	260	3.7	0.2	325	4.4	0.2	864	10.7	0.4	1,677	19.5	0.5	2,351	26.1	0.5	4,030	41.6	0.7	1023%
Localized	3,745	49.5	0.8	4,073	50.1	0.8	5,636	64.7	0.9	7,488	81.8	1.0	8,343	87.6	1.0	9,290	92.3	1.0	86%
Regional	3,570	47.1	0.8	3,735	46.0	0.8	3,919	45.6	0.7	3,678	41.1	0.7	3,445	37.1	0.6	3,899	40.0	0.6	−15%
Distant	708	9.0	0.3	746	8.7	0.3	777	8.6	0.3	742	8.0	0.3	769	8.0	0.3	732	7.2	0.3	−20%
Other/unknown	458	6.2	0.3	572	7.0	0.3	886	10.2	0.3	793	8.5	0.3	674	6.7	0.3	413	3.7	0.2	−41%
Tumor size																			
≤2.0 cm	~	~	~	~	~	~	~	~	~	6,961	76.6	0.9	7,577	80.5	0.9	9,787	98.7	1.0	29%
>2.0 cm	~	~	~	~	~	~	~	~	~	3,811	42.0	0.7	3,804	39.8	0.7	4,340	43.2	0.7	3%
Other/unknown	~	~	~	~	~	~	~	~	~	3,606	40.6	0.7	4,201	45.2	0.7	4,237	42.9	0.7	6%
Lymph nodes																			
Negative	~	~	~	~	~	~	~	~	~	8,667	96.2	1.1	9,962	106.8	1.1	13,566	136.3	1.2	42%
Positive	~	~	~	~	~	~	~	~	~	3,301	37.0	0.7	3,331	36.1	0.6	3,831	39.7	0.6	7%
Other/unknown	~	~	~	~	~	~	~	~	~	2,410	25.5	0.5	2,289	22.7	0.5	967	8.9	0.3	−65%
ER																			
Positive	~	~	~	~	~	~	~	~	~	~	~	~	7,319	76.8	0.9	9,338	93.3	1.0	21%
Negative	~	~	~	~	~	~	~	~	~	~	~	~	2,637	28.8	0.6	2,772	28.6	0.5	−1%
Other/unknown	~	~	~	~	~	~	~	~	~	~	~	~	5,626	59.9	0.8	6,254	63.0	0.8	5%

Key: Rate per 100,000 woman-years age-adjusted (2000 US standard population); SE, standard error; %CH, percentage change in rates; cm, centimeter; ~, not calculated due to substantial unknown data in the earliest years

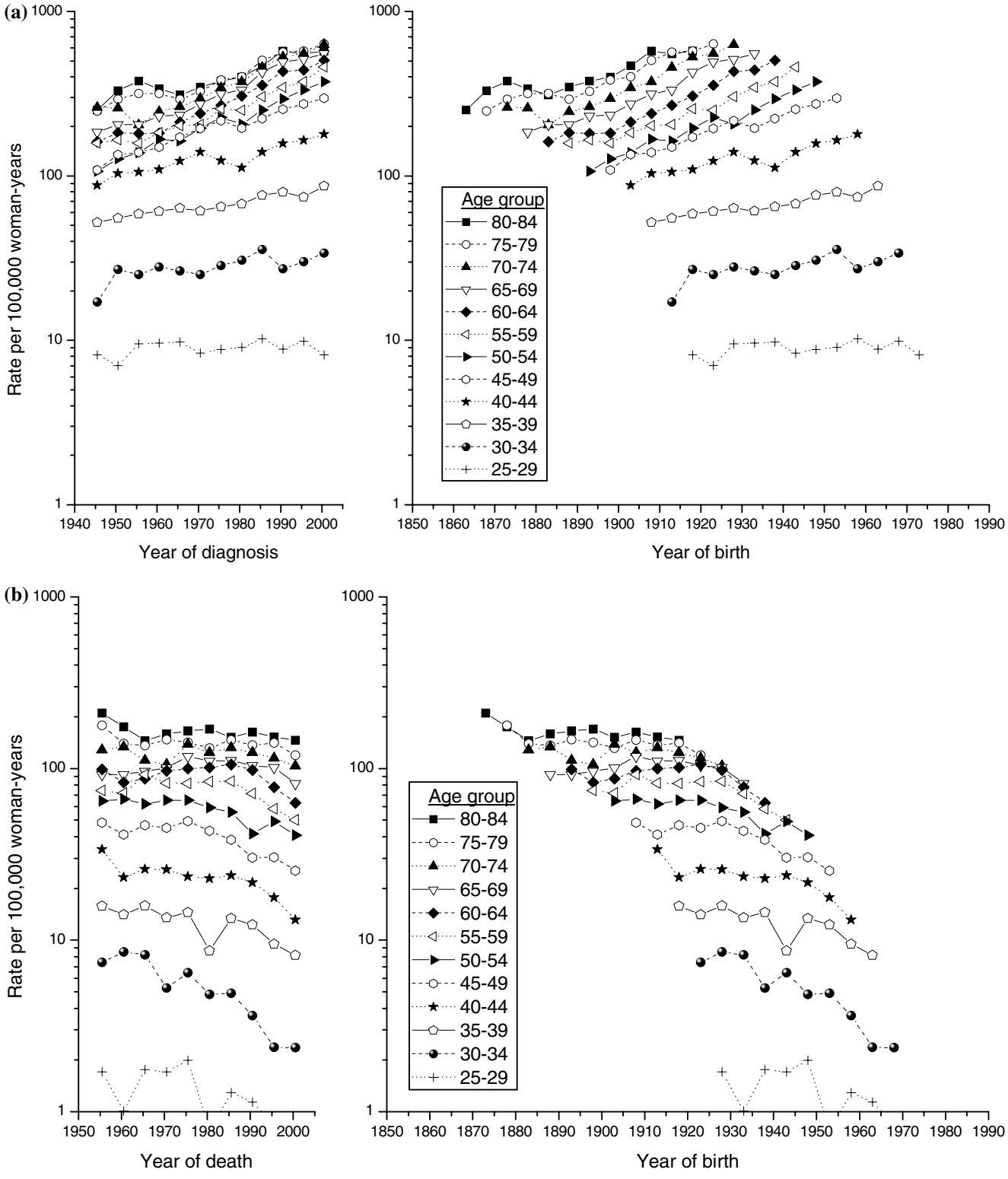

Fig. 2 Female breast cancer age-specific rates in Connecticut for twelve 5-year age groups by calendar period and cohort mid-year of birth. (**a**) Incidence; calendar period (1943–1947 to 1998–2002) and cohort mid-year of birth (circa 1863–1973). (**b**) Mortality; calendar period (1953–1957 to 1998–2002) and cohort mid-year of birth (circa 1873–1973)

breast cancers rose rapidly until age 50 years, and then continued to rise more slowly among older women. Rates rose across all succeeding cohorts (beginning with 1878 and ending with 1958), especially among women targeted for screening, ages 40–80 years.

As mentioned for period-age-specific rates, reliable stage data were not available prior to the 1970s, effectively eliminating consideration of stage-specific rates for the three earliest cohort mid-year of births, i.e., 1878, 1888, 1898. For the remaining six birth cohorts (Fig. 3b), age-specific rates *increased* with age and with each succeeding cohort for *in-situ* and localized stages (beginning with 1908 and ending with 1958), though considerably more dramatically for *in-situ* than localized breast cancers. In contrast, age-specific rates *decreased* modestly with each succeeding cohort for regional and distant stages, though more for regional than distant tumors.

Discussion

Our study is entirely descriptive and should be interpreted with caution. Nonetheless, a direct view of the unique Connecticut Historical Cancer Database (1943–2002) provides population-based breast cancer incidence and mortality estimates before and after widespread screening mammography. Arguably, these kinds of data could not be obtained from other resources such as randomized studies

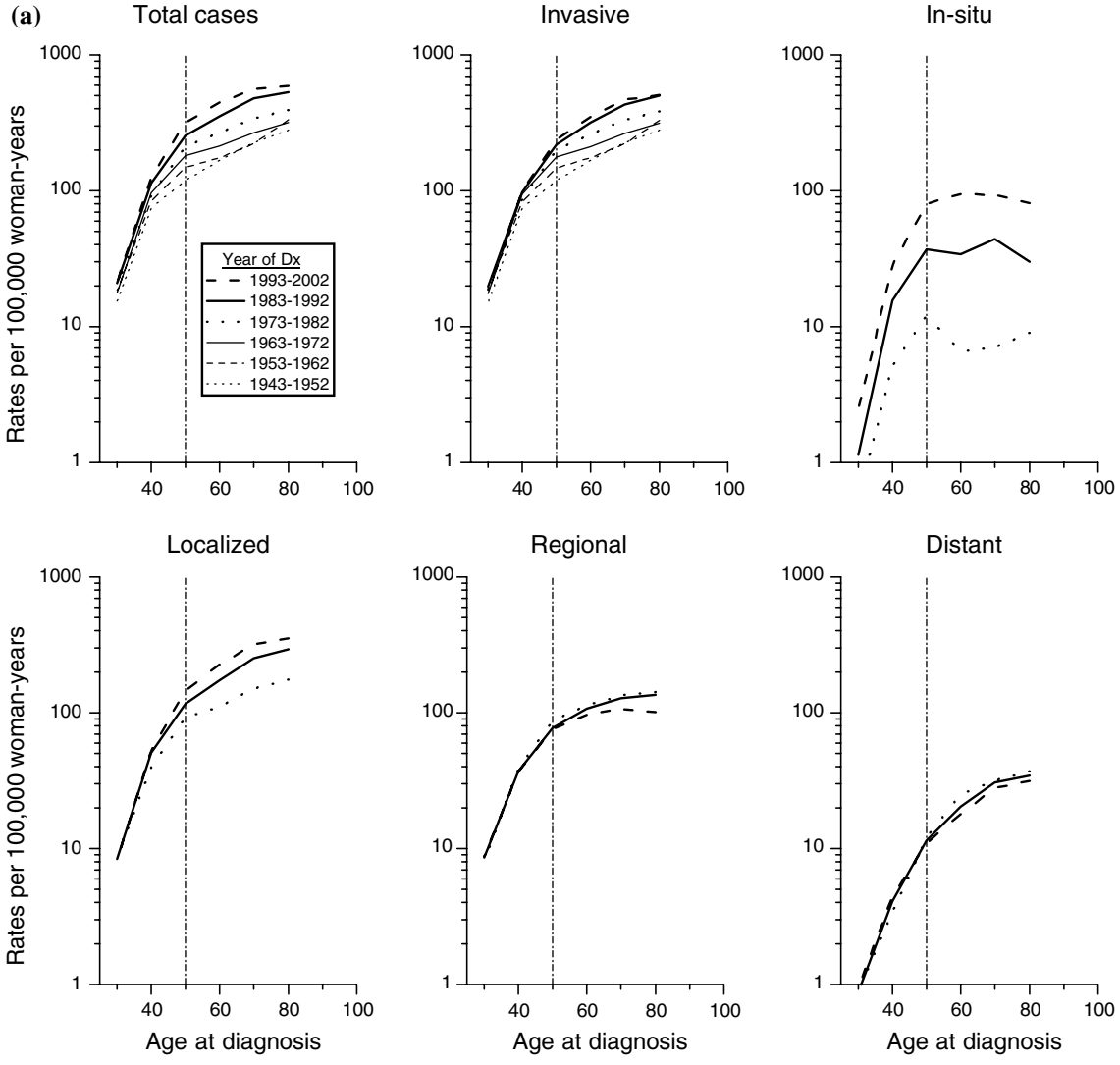

Fig. 3 Female breast cancer age-specific incidence rates in Connecticut by SEER historical stage: (**a**) Period-age-specific rates by six 10-year time periods. Note: reliable stage data were not available prior to 1973, effectively eliminating consideration of stage-specific rates prior to the time period 1973–1977. (**b**) Cohort-age-specific rates by cohort mid-year of birth (circa 1878–1958). Note: reliable stage data were not available prior to 1973, effectively eliminating consideration of stage-specific rates for three earliest birth cohorts (1878, 1888, 1898)

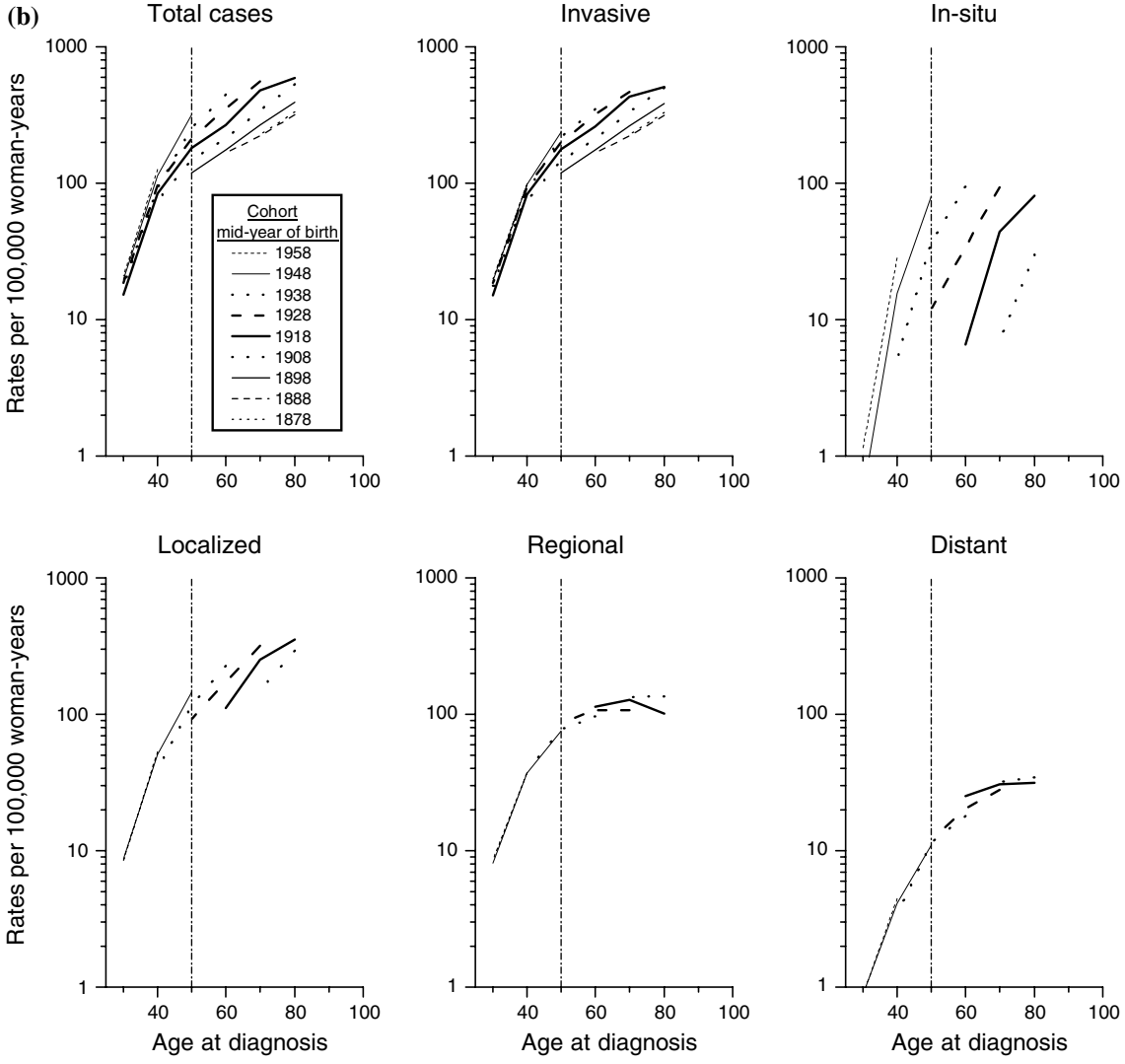

Fig. 3 continued.

and/or mathematical models. Parenthetically, the Connecticut Tumor Registry also appears to be an accurate surrogate for SEER's 9 original registries, with temporal breast cancer trends in Connecticut paralleling those in SEER during the years 1975–2002 (graph not shown). Therefore, a reasonable measure for breast cancer trends in the United States.

Cross-sectional breast cancer incidence rates rose during the entire study period (Fig. 1), undoubtedly due to mixed birth-cohort and screening effects. Of note, overall breast cancer incidence rates increased faster than previously following the widespread use of mammography screening in the early 1980s. Moreover, rates for early-stage and late-stage tumors diverged in the early 1980s, also consistent with earlier detection over time.

Breast cancer mortality rates declined 31.6%, slightly more than estimates from randomized screening trials [1, 2]. Thus, the mortality benefit of early detection and intervention seem firm. However, age-specific breast cancer mortality rates fell even among women too young for routine screening, ages <40 years (Fig. 2b). Additionally, rates declined more slowly for late-stage disease incidence (16%) than for overall breast cancer mortality (31.6%), suggesting at least some improvement in mortality without early detection.

With each succeeding decade and/or birth cohort there was an incremental bulge for total and invasive breast cancer rates among those women targeted for screening (Fig. 3a, b), i.e., ages 40–80 years. There was less effect for younger and older women, who were presumably not screened. Similar age-specific trends have been observed in western Europe, following the introduction of systematic screening mammography in the late 1980s and early 1990s [14, 15].

Age-specific rates also increased dramatically among *in-situ* and localized breast tumors with each succeeding calendar-period and/or birth cohort. More modest reciprocal declines were observed for regional and distant stages. Indeed, decreases in rates for distant disease are barely discernable on the log-linear scale.

The very large increases of early-stage disease (*in-situ* and localized) may be partly attributable to changing diagnostic criteria and/or systematic biases, i.e., lead-time and length biases [7, 8, 16, 17]. Lead-time bias refers to a stage shift (detecting tumors at an earlier stage) or a backward shift within stage. Length bias refers to the detection of indolent tumors, some of which may pose no threat to life. Indeed, mammography-detected breast cancers are more likely to have indolent tumor characteristics such as smaller sizes, negative lymph nodes, good grade, and positive hormone receptors (Table 1), and are less likely to have aggressive tumor features such as increased proliferative rates, dense breast tissue, basal cellular phenotype, HER2 and p53 expression [16, 18–22].

In sum, it has long been shown that mammography screening results in a significant increase in the diagnosis of *in-situ* lesions [23]. We must now ponder whether (and to what extent) early detection also may result in the increased diagnosis of occult and localized breast cancer with low malignant potential, as previously suggested by Fox and Adami even before widespread screening [5, 6]. What Fox and Adami speculated prior to widespread screening mammography is even more relevant with improved methods of early detection. Indeed, newer screening technologies such as digital mammography and magnetic resonance imaging may further increase the detection rate of occult and indolent breast tumors.

It would be a disservice to patients and physicians alike for our remarks to discourage early breast cancer detection. However, given the risk of diagnosing and treating biologically indolent early-stage lesions, the aggressive search for early-stage lesions will also require improved methods and/or algorithms to distinguish indolent from aggressive disease.

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