

Breast Cancer Incidence, 1980–2006: Combined Roles of Menopausal Hormone Therapy, Screening Mammography, and Estrogen Receptor Status

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- Background** Breast cancer incidence has been rising since at least 1935–1939, but recent US data reveal a statistically significant decline in breast cancer incidence in 2003 that persisted through 2004. Identifying the specific contributions of the potential causes of this long-term increase and the recent decrease in incidence has been challenging. Marked changes in rates of mammography screening and use of menopausal hormone therapy since 1980 have added further complexity. We examined the potential association between menopausal hormone therapy use and recent changes in breast cancer incidence.
- Methods** Using tumor registry, clinical, pathology, and pharmacy data from Kaiser Permanente Northwest, a large prepaid US health plan, we compared age-specific and age-adjusted breast cancer incidence rates (2-year moving averages) with use of screening mammography and dispensed menopausal hormone therapy prescriptions between 1980 and 2006. Temporal changes in incidence rates were assessed via joinpoint regression.
- Results** A total of 7386 incident invasive breast cancers were diagnosed in plan members from 1980 through 2006. Overall age-adjusted breast cancer incidence rates per 100 000 women rose 25% from the early 1980s (105.6) to 1992–1993 (131.7) and an additional 15% through 2000–2001 (151.3), then dropped by 18% to 2003–2004 (123.6) and edged up slightly in 2005–2006 (126.2). These patterns were largely restricted to women aged 45 years or older and to estrogen receptor–positive (ER+) breast cancers. Incidence rates of ER-negative tumors experienced neither of the rises seen for ER+ tumors but also fell precipitously from 2003 through 2006. Rates of mammography screening sharply increased from 1980 to 1993 but then leveled off, and 75%–79% of women aged 45 years or older received a mammogram at least once every 2 years from 1993 through 2006. Menopausal hormone therapy dispensings, particularly of estrogen-plus-progestin formulations, increased from 1988 to 2002 but then dropped by approximately 75% after 2002.
- Conclusions** From 1980 through 2006, quantitative and qualitative trends in breast cancer incidence rates, particularly for ER+ tumors, parallel major changes in patterns of mammography screening and use of menopausal hormone therapy.

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Breast cancer incidence rates have risen since at least 1935–1939 (1). In 1990, we reported (2) that breast cancer incidence had increased among women aged 60 years or older at diagnosis and for estrogen receptor–positive (ER+) breast cancers between 1960 and 1985 in the Kaiser Permanente Northwest (KPNW) prepaid health plan. We discussed various possible explanations, including changes in reproductive risk factor profiles over time, the introduction of screening mammography, and growing use of menopausal hormone therapy. It was unclear whether these were sufficient to explain the patterns observed.

After 1985, rates of screening mammography in the United States continued to increase (3), and breast cancer incidence rates began to reflect the effects of widespread screening. During the same period, the types of menopausal hormone therapy prescribed expanded from unopposed estrogen to estrogen plus progestin, the numbers of dispensed menopausal hormone therapy prescriptions

increased dramatically, and menopausal hormone therapy use expanded from primarily treatment for menopausal symptoms to more widespread use for potential chronic disease prevention (4). At the same time, epidemiologic studies continued to document strong, statistically significant increased risks of breast cancer in

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women who used menopausal hormone therapy compared with women who never used it (5–7).

In July 2002, the Women's Health Initiative (WHI) estrogen-plus-progestin trial, a randomized, double-blinded, placebo-controlled clinical trial of estrogen-plus-progestin use among postmenopausal women for primary prevention of chronic disease was stopped early because risks exceeded benefits (7). Increased risks of breast cancer among the women assigned to take estrogen plus progestin contributed specifically to the conclusion that overall health risks exceeded benefits of use of estrogen plus progestin in the WHI. After the release of these WHI findings, menopausal hormone therapy use by American women substantially declined in 2003 (8). Recently released data from the National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) program showed a marked, statistically significant decline in breast cancer incidence in 2003 and 2004, after showing smaller and non-statistically significant declines starting in 1999 (9). This finding sparked speculation that the widespread cessation of menopausal hormone therapy use after the WHI was responsible for the drop in breast cancer incidence because fewer women taking menopausal hormone therapy would mean fewer women exposed to the increased breast cancer risk that accompanies use of estrogen plus progestin (10).

Between 2000 and 2005, nationwide use of screening mammography fell by 4% overall among women aged 40 years or older and by almost 7% among women aged 50–64 years (11). Despite strong circumstantial evidence for a link between recent changes in menopausal hormone therapy use and lower nationwide breast cancer incidence, the recent changes in mammography use and the absence of data from single, defined populations in which one could directly evaluate all three factors—breast cancer incidence, menopausal hormone therapy use, and mammography—have raised questions about the determinants of the recent decline in US breast cancer incidence rates. To address these questions, we assessed data on breast cancer incidence, dispensed menopausal hormone therapy prescriptions, and screening mammography at KPNW, a large, prepaid health plan. Incorporating data through December 31, 2006, also permits an assessment of more recent patterns than are available in the NCI SEER program.

Subjects and Methods

Data Source

Our study population comprised female KPNW members who participated in the plan from January 1, 1980, to December 31, 2006. Members receive essentially all preventive and therapeutic care from KPNW physicians at KPNW-owned hospitals or at leased beds in local facilities. Virtually all cancer care occurs within these KPNW facilities under the direction of KPNW physicians. The racial/ethnic distribution of KPNW members (approximately 82% white, 3% African American, 5% Asian American, 5% Hispanic, and 5% other) (12) reflects that of the surrounding Portland, OR, metropolitan area and has not substantially changed during the study period. Since 1982, KPNW has included Medicare enrollees. Medicare members account for 13%–15% of the KPNW population, are fully integrated into the health plan, and receive care that is identical to that received by non-Medicare members of KPNW.

CONTEXT AND CAVEATS

Prior knowledge

The incidence of breast cancer in the United States has risen steadily in recent decades through 2003, when incidence began to decline. Rates of menopausal hormone therapy use and screening mammography have also changed over time, and the relative contributions of these factors to the incidence of breast cancer is unclear.

Study design

Analysis of time trends in breast cancer incidence, dispensed menopausal hormone therapy prescriptions, and screening mammography use among women enrolled in a large health plan from 1980 through 2006.

Contribution

In women aged 45 years and older, age-adjusted incidence of breast cancer (mainly estrogen receptor-positive) rose from the early 1980s through 2001, then dropped by 18% from 2003 through 2006. Menopausal hormone therapy dispensings increased from 1988 to 2002 and then dropped by 75%. Rates of mammography screening increased from 1980 through 1993 and then remained largely stable through 2006.

Implications

The rise in breast cancer incidence rates through the late 1990s is consistent with the effects of mammography screening and increasing use of menopausal hormone therapy, and the recent decline in incidence is consistent with the drop in hormone use.

Limitations

This descriptive, population-level study examined aggregate data, so changes in other unmeasured risk factors could theoretically explain the observed incidence patterns.

The inclusion of Medicare patients has increased the percentage of older women in KPNW. Since 1986, women aged 45–59 years old and women aged 60 years or older have constituted 25% and 20%, respectively, of the KPNW female population, which reached 255 171 on June 30, 2006. Approximately 15% of members leave the KPNW plan each year, but the actual number of plan members has increased every year for nearly 60 years. Almost all non-Medicare KPNW members receive employer-based health insurance.

The KPNW system includes computerized administrative, clinical, mammography, and pharmacy databases that allow linkage of several sources of data for all members of the plan. KPNW also maintains a tumor registry that has been fully integrated into these data systems since 1970. Repeated audits in conjunction with continuing accreditation surveys every 3 years by the Commission on Cancer of the American College of Surgeons have verified 95%–98% ascertainment of all newly diagnosed cancers among KPNW members.

Using the KPNW tumor registry files, we identified all incident primary invasive breast cancers that were diagnosed among KPNW plan members between January 1, 1980, and December 31, 2006. All cases are routinely coded from the pathology reports according to the current edition of the International Classification of Diseases for Oncology (ICD-O).

This study was reviewed and approved, under a waiver of written informed consent, by the KPNW Center for Health Research's Research Subjects Protection Office.

Pathology

The KPNW Department of Pathology reviews pathology specimens from all newly diagnosed cancers, including those from the approximately 15% of KPNW members who are initially diagnosed at community hospitals. The Department works largely in a single central location with frequent consultations, collaborative quality reviews, and requisite quality assurance activities.

Hormone Receptor Status

Tumor specimens from KPNW patients have been analyzed for estrogen receptor (ER) status since the mid-1970s. Assays were performed at the Oregon Health and Science University from 1980 through 1990, at Nichols Laboratory from 1991 through 1997, and at the KPNW Laboratory since 1998. All laboratories passed quality reviews of the NCI-sponsored clinical cooperative groups for accuracy and quality of receptor measurement. The reagents for, methods of staining of, and analysis and definitions of positive and negative reporting of immunohistochemistry-based ER status by KPNW pathologists have not changed since 1998. The percent of tumors analyzed for ER status increased from 67% in 1980 to 81% in 1989, 89% in 1994, and 99% in 2006.

Mammography Rates

The computerized Radiology Information Management system (RIM) at KPNW records every radiologic procedure among KPNW members. Mammograms at KPNW are coded as either "screening" or "diagnostic." During the entire study period (1980–2006), KPNW general radiology benefits have covered all mammograms at KPNW facilities. Mammograms at other facilities are neither covered nor reimbursed, so RIM captures essentially all mammograms received by KPNW members. We used population figures from KPNW administrative files to calculate annual percentages of female KPNW members who received screening mammography between 1980 and 2006. We calculated annual age-specific proportions (for women aged 45–59 years and ≥ 60 years) of KPNW members who received screening mammography by dividing the total number of screening mammograms performed at KPNW each year by the total number of women in that age group in KPNW. For 1992–2006, we also obtained KPNW-computed rates for the percent of women receiving a mammogram at least once every 2 years; such data are required of health plans reporting in the Health Plan Employer Data and Information Set.

Pharmacy Data

Kaiser Permanente operates a large in- and outpatient pharmacy system that serves KPNW members throughout the region. More than 70% of KPNW members had pharmacy benefits after 1987, and 93%–97% of members had them after 1993. Members who fill prescriptions at non-KPNW pharmacies must pay full price for medications, which means that essentially all prescriptions were filled at KPNW.

Since 1987, The Outpatient Pharmacy System (TOPS) at KPNW has tracked all medications obtained by KPNW members

by recording each drug and dose dispensed. We queried TOPS for the numbers of prescriptions dispensed by KPNW pharmacies between 1988 and 2006. We used the number of oral estrogen or oral estrogen-plus-progestin prescriptions dispensed by KPNW pharmacies to calculate annual age-specific proportions of KPNW members who received at least one estrogen or estrogen-plus-progestin prescription. Members who filled multiple prescriptions for these medications during the year were counted only once for each particular medication.

Until 2005, almost all estrogens dispensed at KPNW pharmacies were oral conjugated equine estrogens, with only a small percentage of women receiving prescriptions for oral micronized estradiol. Starting in 2005, estradiol replaced conjugated equine estrogens as the predominant oral estrogen dispensed at KPNW pharmacies. Estrogen plus progestin was prescribed as two separate prescriptions, one for these oral estrogens and one for oral medroxyprogesterone acetate (MPA). KPNW physicians have only rarely prescribed unopposed MPA or the single tablet that contains both estrogen and MPA. Therefore, the number of dispensed oral "progestins" accurately estimates the number of dispensed estrogen-plus-progestin prescriptions. We estimated the number of dispensed prescriptions for unopposed estrogen by subtracting the number of dispensed progestins from the number of dispensed estrogens.

Statistical Analysis

Health plan membership counts provided the population figures for calculating incidence rates. Both age-specific and age-adjusted incidence rates of invasive breast cancer were calculated, with the adjusted rates standardized by the direct method to the US 2000 standard population (13). Rates are expressed per 100,000 women per year and presented as 2-year moving averages to reduce random variation. All figures are displayed according to the recommendations of Devesa et al. (14).

We assessed temporal changes in incidence rates via joinpoint regression (15), a method of weighted least squares log-linear regression analysis that uses joined straight-line segments to identify time points at which statistically significant changes in incidence rates occur (16). For trends in breast cancer incidence rates by age group and ER status, we fit joinpoint regression models with up to three joinpoints (i.e., up to four straight-line segments) and chose the best-fitting model based on permutation tests that were adjusted for multiple comparisons to maintain an overall two-sided *P* value of less than .05. After the number of joinpoints was identified, each joined line segment was expressed as an annual percentage change (APC) with a corresponding 95% confidence interval (CI). We used the 2-year moving average incidence rates to identify the best-fitting model (i.e., to identify the time points at which statistically significant changes in breast cancer incidence occurred) and to calculate the APCs.

Results

Breast Cancer Incidence at Kaiser Permanente Northwest

A total of 7386 female KPNW members were diagnosed with invasive breast cancer from 1980 through 2006. Of these 7386 breast cancers, 5742 (78%) were classified as infiltrating ductal

Table 1. Distribution of incident invasive breast cancers diagnosed among KPNW health plan members by histology designation and ICD-O-3 codes, 1980–2006*

ICD-O-3 code	Histology designation	No. of diagnoses	% of total
8500/3	Infiltrating duct carcinoma, NOS	5742	77.7
8520/3	Lobular carcinoma, NOS	570	7.7
8522/3	Infiltrating duct and lobular carcinoma	354	4.8
8523/3	Infiltrating duct mixed with other types of carcinoma	62	0.8
8140/3	Adenocarcinoma, NOS	92	1.2
8480/3	Mucinous adenocarcinoma	164	2.2
8211/3	Tubular adenocarcinoma	104	1.4
8010/3	Carcinoma, NOS	36	0.5
8020/3	Carcinoma, undifferentiated	11	0.1
8050/3	Papillary carcinoma, NOS	13	0.2
8501/3	Comedocarcinoma, NOS	26	0.4
8510/3	Medullary carcinoma, NOS	42	0.6
8530/3	Inflammatory carcinoma	75	1.0
8541/3	Paget disease and infiltrating duct carcinoma	19	0.3
All other types		76	1.0
Total		7386	

* KPNW = Kaiser Permanente Northwest; ICD-O-3 = International Classification of Diseases for Oncology, Third Edition; NOS = not otherwise specified.

carcinoma and 570 (7.7%) as invasive lobular carcinoma (Table 1). The percentage of pure lobular carcinoma was relatively constant over time, whereas the percentage of infiltrating ductal carcinoma declined from 85% in 1986 to 72% in 2000–2006. The declining percentage of infiltrating ductal carcinoma seems likely due to the introduction of new codes, which allowed combination diagnoses of infiltrating ductal carcinoma with other histologies, in the Second and Third Editions of the ICD-O. These categories did not exist in the 1980s but accounted for 10.9% of the breast cancer diagnoses in 2000–2006.

The overall incidence of breast cancer was relatively constant in the early 1980s (age-adjusted annual rate of 105.6 per 100 000 women), rose dramatically from 1982–1983 through 1986–1987, dropped slightly from 1987–1988 through 1989–1990, and then resumed its rise to a peak in 1990–1991 (132.3 per 100 000; Fig. 1). After another short decline, rates then rose steadily through 2000–2001 (151.3 per 100 000). There was a small decline to 2001–2002 and an abrupt decline from 2001–2002 to 2003–2004, after which rates stabilized through 2005–2006. The average rise in the annual rate from the early 1980s to 1992–1993 (2.7 cases per 100 000 women) was similar to the rise from 1992–1993 to 2000–2001 (2.4 cases per 100 000). However, because of the steadily rising incidence rates, the proportional increase was greater from 1982–1983 to 1992–1993 (28%) than from 1992–1993 to 2000–2001 (15%). The 2-year moving average incidence rates of invasive breast cancer in 2003–2004 (123.6 per 100 000), 2004–2005 (128.4), and 2005–2006 (126.2) were comparable to rates last seen in 1984–1985 (124.1).

The joinpoint regression analysis confirmed these patterns and identified three years at which statistically significant changes in breast cancer incidence rate trends occurred: 1983, 1986, and 2001. When expressed as APCs, incidence rates fell 1.8% per year (95%

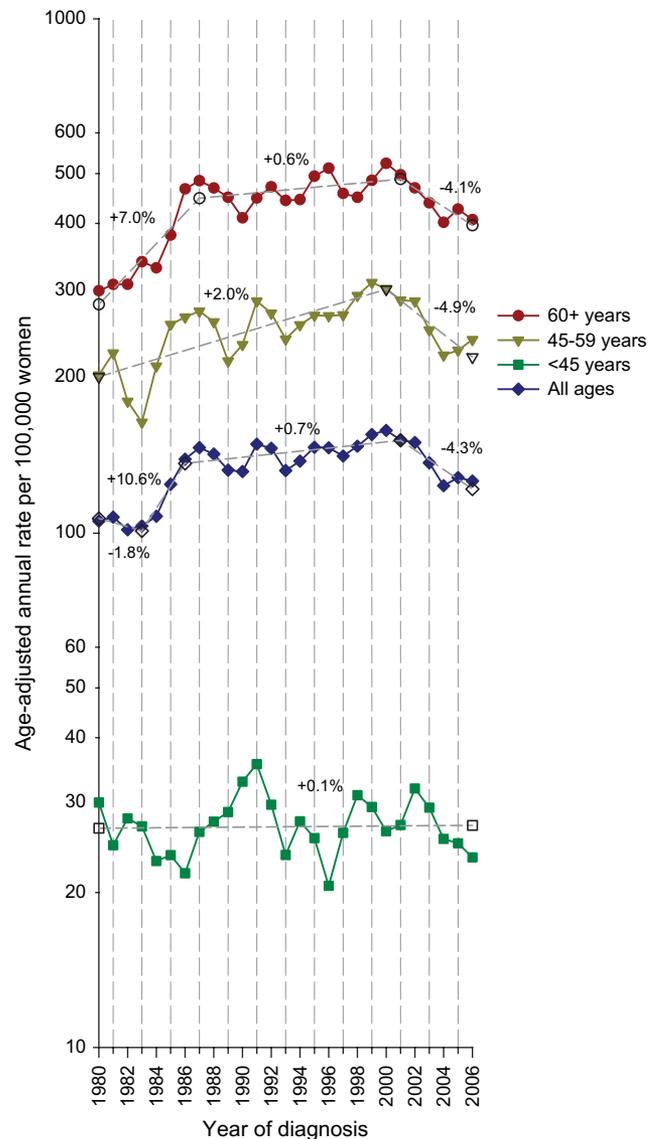


Fig. 1. Age-adjusted annual incidence rates for invasive breast cancer at Kaiser Permanente Northwest (KPNW), 1980–2006, for all ages and for age groups. **Data points** reflect 2-year moving averages, based on the KPNW tumor registry and KPNW administrative files of female health plan members, with the individual-year data reflecting the 2-year moving average of that year plus the previous year (e.g., 1990 data point reflects 2-year moving average from 1989 through 1990). Joinpoint regression and annual percentage changes in incidence are superimposed on incidence plots. **Open symbols** represent statistically significant changes in incidence (i.e., joinpoints), based on joinpoint regression; dashed lines represent straight-line segments between joinpoints. Adjacent numbers represent annual percentage changes for those segments.

CI = –8.6% to 5.6%) from 1980 to 1983, increased 10.6% per year (95% CI = 4.2% to 27.9%) from 1983 to 1986, increased 0.7% per year (95% CI = 0.01% to 1.4%) from 1986 to 2001, and then declined 4.3% per year (95% CI = –7.2% to –1.1%) from 2001 to 2006.

Age-Specific Incidence Rates

For women younger than 45 years of age, there was essentially no change in incidence rates of invasive breast cancer over the 27-year period (Fig. 1). Incidence rates increased both among women aged 45–59 years and women aged 60 years and older. From the early 1980s to 1992–1993, incidence rates increased more rapidly among

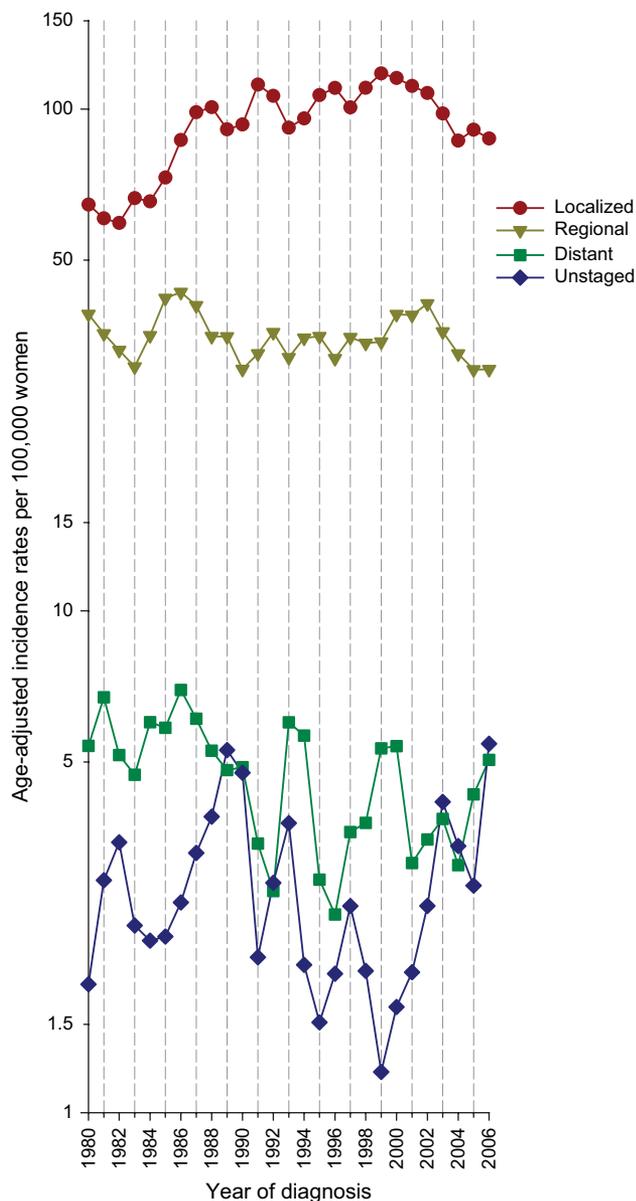


Fig. 2. Age-adjusted annual incidence rates for invasive breast cancer at Kaiser Permanente Northwest (KPNW), 1980–2006, by stage of disease at diagnosis. Data points reflect 2-year moving averages, based on the KPNW Tumor Registry and KPNW administrative files of female health plan members.

women aged 60 years and older (39%) than among women aged 45–59 years (19%). From 1992–1993 to 2002–2003, incidence rates increased more rapidly among women aged 45–59 years (19%) than among women aged 60 years and older (12%).

Joinpoint regression analyses also confirmed these patterns. There were no statistically significant changes in incidence rate trends for women younger than 45 years of age, one statistically significant change for women aged 45–59 years (at 2000), and two statistically significant changes for women aged 60 years or older (at 1987 and 2001). Expressed as APCs, these changes reflected a 2.0% (95% CI = 1.1% to 2.8%) increase per year between 1980 and 2000 and a 4.9% (95% CI = –9.7% to 0.1%) decrease per year between 2000 and 2006 for women aged 45–59 years. For women aged 60 years or older, the best-fitting model showed a 7.0% (95%

CI = 4.4% to 9.7%) increase per year between 1980 and 1987, a 0.6% (95% CI = –0.3% to 1.6%) increase per year from 1987 to 2001, and a 4.1% (95% CI = –7.9% to –0.03%) decrease per year from 2001 to 2006.

Stage-Specific Incidence Rates

Increasing rates of cancers diagnosed at localized stages—essentially node-negative cancers confined to the breast—accounted for almost all the overall rate increase from 1980 through 1998–1999 (Fig. 2). Rates of regional-stage tumors (either locally invasive beyond the breast or with spread to axillary nodes) remained nearly constant through 2001–2002. Rates of both localized tumors and regional-stage tumors fell in the 2000s. The rates of distant-stage tumors steadily declined between 1980 and 2006.

Estrogen Receptor Status

There were dramatic differences in the incidence rate trends by ER status (Fig. 3). ER+ tumors closely followed the pattern found for all breast cancers, including the recent decline from 1999–2000 through 2005–2006. Similar overall patterns were noted for ER+ ductal cancers and ER+ lobular cancers, with larger relative increases seen for lobular tumors (data not shown).

The three joinpoints (1983, 1986, and 2001) for statistically significant changes in ER+ incidence rate trends were the same as those for overall breast cancer incidence rate trends. Expressed as APCs, these four trends reflected a 5.0% (95% CI = 3.7% to 14.4%) annual increase from 1980 to 1983, a 18.9% (95% CI = 0.1% to 41.2%) annual increase from 1983 to 1986, a 2.1% (95% CI = 1.2% to 2.9%) annual increase from 1986 to 2001, and a 2.7% (95% CI = –6.4% to 1.1%) annual decrease from 2001 to 2006.

In contrast to the incidence rates trends for the ER+ tumors, those for ER–negative (ER–) tumors, which were based on fewer cases and were somewhat more variable, showed no evidence of an increase over the entire 27-year period. Instead, incidence rates fluctuated but declined overall throughout the 1980s and then remained level throughout much of the 1990s until an abrupt decline after 1999. This latter decline showed no evidence of abating, dropping steadily from 24.0 per 100 000 women in 2002–2003 to 15.9 per 100 000 in 2004–2005 and 16.6 per 100 000 in 2005–2006. The APCs for ER– incidence rates were –2.1% (95% CI = –3.2% to –1.0%) from 1980 to 1995, 3.7% (95% CI = –9.0% to 18.1%) from 1995 to 1999, and –9.8% (95% CI = –12.8% to –6.6%) from 1999 to 2006.

Mammography

Screening mammography was not common at KPNW before 1982; less than 5% of women aged 45 years or older underwent the procedure each year (Fig. 4). Beginning in 1983, the proportion of women receiving annual mammography rose rapidly to approximately 25% in 1986. After a brief plateau in 1986–1987, the proportion rose to 48.1% (95% CI = 47.6% to 48.7%) in 1991 among women aged 45–59 years and 46.0% (95% CI = 45.5% to 46.5%) in 1998 among women aged 60 years or older. These proportions then stabilized until 2000, fell to 44%–45% in both age groups between 2001 and 2004 but then rose to 46.6% (95% CI = 46.2% to 47.0%) among women aged 45–59 years and 48.0% (95% CI = 47.6% to 48.5%) among women aged 60 years or older in 2006. For each year

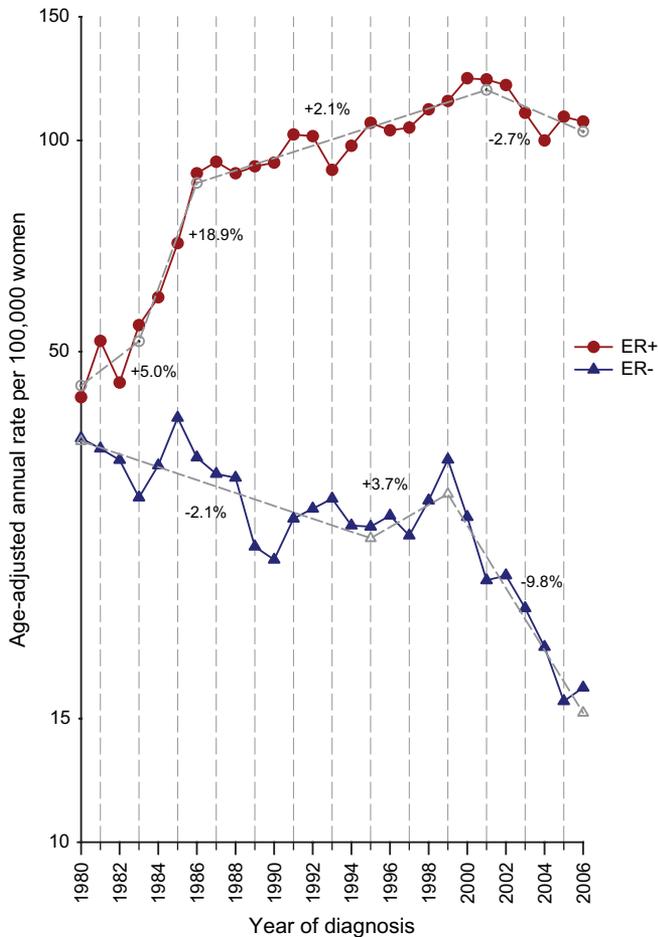


Fig. 3. Age-adjusted annual incidence rates for invasive breast cancer at Kaiser Permanente Northwest (KPNW), 1980–2006, by estrogen receptor (ER) status. Data points reflect 2-year moving averages, based on the KPNW Tumor Registry and KPNW administrative files of female health plan members, with the individual-year data reflecting the 2-year moving average of that year plus the previous year (e.g., 1990 data point reflects 2-year moving average from 1989 to 1990). Joinpoint regression and annual percentage changes (APCs) in incidence are superimposed on incidence plots. Not shown are incidence rates for invasive breast cancers with unknown ER status, which made up 33% of all breast cancers in 1980, 19% of all breast cancers in 1989, 11% of all breast cancers in 1994, and less than 1% of all breast cancers in 2006, when ER status was unknown for only one breast cancer diagnosed at KPNW. **Open symbols** represent statistically significant changes in incidence (i.e., joinpoints), based on joinpoint regression. **Dashed lines** represent straight-line segments between joinpoints. **Adjacent numbers** represent APCs for those segments.

between 1993 and 2006, 75%–79% of women older than 45 years of age had a screening mammogram within the past 2 years.

Menopausal Hormone Therapy

In 1988, shortly after TOPS began, 13.9% (95% CI = 13.5% to 14.4%) of women aged 45–59 years and 14.5% (95% CI = 14.1% to 14.9%) of women aged 60 years or older were dispensed unopposed estrogens. The respective percentages for MPA were 14.1% (95% CI = 13.7% to 14.5%) and 4.7% (95% CI = 4.5% to 5.0%), respectively. The percentage of women aged 45–59 years dispensed an estrogen or progestin prescription steadily rose for 8 years until 1995 and then leveled off through 2001 (Fig. 5). The percentage of women aged 45–59 years dispensed unopposed

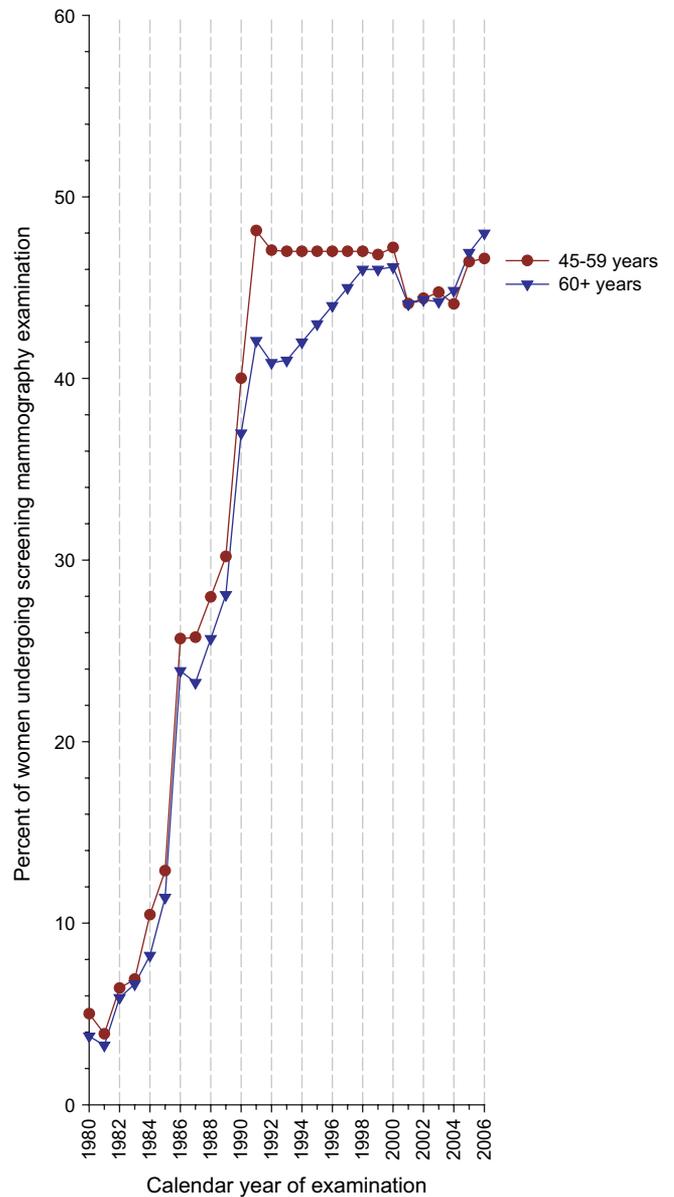


Fig. 4. Percentage of female Kaiser Permanente Northwest (KPNW) members aged 45 years or older who received at least one screening mammography examination per year, 1980–2006, by age group (45–59 years versus 60 years or older). Data are from KPNW Radiology Information Management system, which records all radiologic procedures among KPNW members. Screening mammograms do not include diagnostic mammograms.

estrogen prescriptions peaked at 21.1% (95% CI = 20.7% to 21.6%) in 1994, a level 64% higher than the 1988 level. Over the same period, MPA dispensings rose approximately 80% overall. For women aged 60 years or older, unopposed estrogen dispensings rose 90% and MPA dispensings rose 270% through 1999, when both leveled off. Unopposed estrogen dispensings continued to rise among older women after plateauing among younger women, such that in 2000, dispensings among older women surpassed dispensings among younger women. Although MPA dispensings also rose sharply among older women during the 1990s, dispensings remained appreciably higher in younger women. Compared with 1999, when 21.7% (95% CI = 21.5% to 22.0%) of

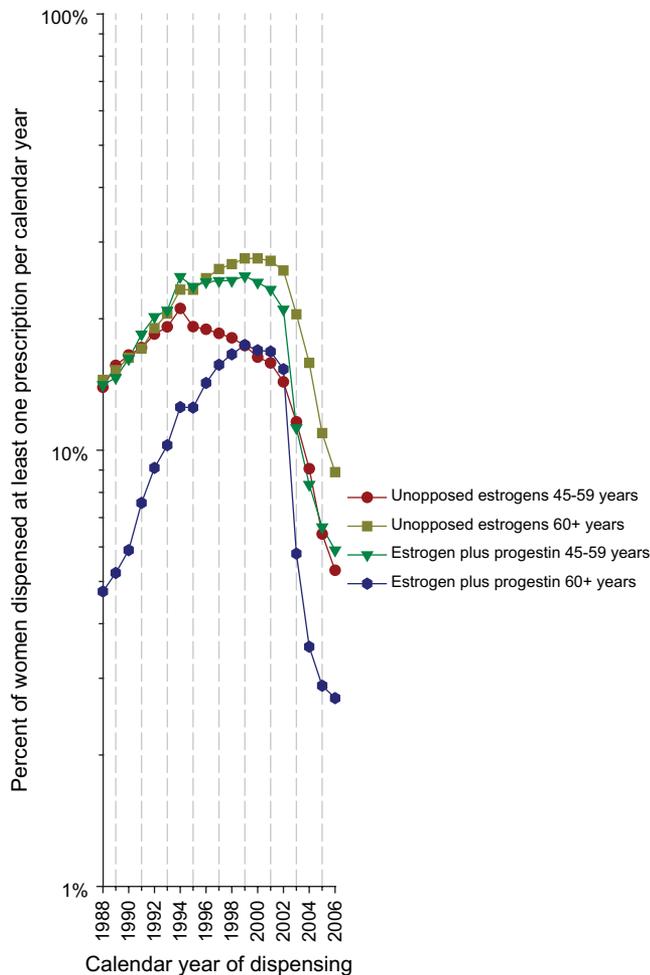


Fig. 5. Percentage of female Kaiser Permanente Northwest (KPNW) members who were dispensed at least one unopposed estrogen or estrogen-plus-progestin prescription per year, 1988–2006, by age group. Data are from the KPNW Outpatient Pharmacy System, which tracks each drug dispensed at KPNW-owned and -operated pharmacies.

women aged 45 years or older were dispensed prescriptions for unopposed estrogens, unopposed estrogen dispensings were 5% lower in 2001, 11% lower in 2002, 29% lower in 2003, and 69% lower in 2006. Estrogen-plus-progestin dispensings among women aged 45 years or older peaked in 1999 at 21.8 (95% CI = 21.5% to 22.1%) but were 6% lower in 2001, 15% lower in 2002, 59% lower in 2003, and 79% lower in 2006.

Neither tamoxifen nor raloxifene was widely dispensed at KPNW during the study period. In women aged 45–59 years, tamoxifen dispensings increased from 0.1% in 1988 to 0.9% in 1994 and then remained stable at 0.8%–1.1% through 2006. In women aged 60 years or older, dispensing rose from 0.5% in 1988 to 1.9% in 1992 and then remained stable (1.8%–2.3%) through 2006. Between 1998 and 2006, raloxifene was dispensed to 0.06%–0.21% of women aged 45–59 years and 0.09%–0.41% of women aged 60 years or older.

Discussion

We previously described (1) a steady rise in breast cancer incidence rates among older women enrolled in KPNW from the early

1960s to early 1980s, which seemed, at least in the later years, to be restricted to ER+ tumors (2). In our update and expansion of these data, we observed three major patterns. First, breast cancer incidence rates rose markedly—by 28% overall—from 1982–1983 (when rates were 103.2 per 100 000) to 1992–1993 (131.7). Second, after slightly declining, the rates then rose steadily but more slowly—by 15% overall—through 2000–2001 (151.3). Finally, the rates dropped dramatically—by 18%—through 2004 and then leveled off through 2006 (126.2). Rates as low as these were last observed in the mid-1980s.

The rise in incidence rates throughout the 1980s and early 1990s is qualitatively and quantitatively consistent with the simultaneous adoption of screening mammography at KPNW. The proportion of women regularly screened progressively rose from a few percent in 1980 to 75% after 1993. In general, populations into which screening mammography is introduced demonstrate increased breast cancer incidence rates from three sources. Initially, women undergoing their first screen experience a major increase in rate due to the detection of prevalent, small, slow-growing tumors that have accumulated over several years. This “prevalence” rate, in the first year of screening, is generally 50%–100% higher than that seen in unscreened populations (17,18).

The incidence rates in screened populations decline following the initial screening but plateau at rates higher than those in unscreened populations because of two other sources of increase. First, as a result of the lead time introduced by screening, age at diagnosis declines, on average, by 2–4 years. Second, some tumors that might never have come to clinical recognition without mammography—particularly small, slower-growing tumors—are detected (i.e., “overdiagnosis” or length-time bias). Although the presence of these two sources of increased breast cancer incidence in screened populations is generally accepted, their quantitative effect on breast cancer incidence rates is controversial; estimates range from a 10% to a 50% excess compared with incidence in unscreened populations (18,19).

We believe that the rapid rise in breast cancer rates up to the early 1990s seen in the KPNW reflects these three sources of increase, with the slight decline at that point marking the exhaustion of large numbers of previously unscreened women undergoing prevalence examinations. The new baseline rate, which is approximately 30% higher than the baseline rate seen before screening began in the early 1980s, is consistent with, albeit at the higher end of, the estimates for the excess expected due to lead time and overdiagnosis in screened women (i.e., a 30% overall increase translates to a 40% increase in the 75% of the population being screened).

Not only is the total rise in incidence rates that we observed in KPNW women through the early 1990s consistent with screening effects, but the characteristics of the rise are as well. Rapidly rising rates from the early 1980s (103.2 in 1982–1983) through 1987 (146.3 in 1986–1987) closely correspond to the concurrent sharp initial increase in mammography screening. The subsequent temporary plateauing of screening rates occurred at the same time as the pause in increase in annual mammography screening, and the subsequent rise in cancer rates, albeit at a lower pace than the initial rise, mimicked the final twofold rise in mammography. The greater rise in breast cancer incidence rates

among women aged 60 years or older than women aged 45–59 years is also consistent with screening effects: older women have had more years to both accumulate prevalent tumors and have detected tumors that, in the absence of screening, would have been undetected before they died of other causes. Other factors, such as increasing menopausal hormone therapy use, may have contributed to the rise in rates during the 1980s, particularly because the total increase is at the upper end of what might be expected from mammography alone. However, the substantial influence of screening complicates attempts to quantify effects of other factors.

By the early 1990s, the percentage of the population receiving screening mammograms leveled off, which essentially rules out mammography as an explanation for the second rise in incidence (from 132.3 in 1989–1990 to 155.3 in 1998–1999) or the steep drop in incidence from 2001–2002 (150.5) through 2005–2006 (126.2). Instead, these trends parallel increased use of menopausal hormone therapy, particularly estrogen plus progestin, at KPNW throughout the 1990s, until menopausal hormone therapy use slightly declined in 2000–2002 and dramatically dropped in 2003. Similar usage patterns have been observed in other populations (8,20,21) and are likely related to reports from two clinical trials [the Heart and Estrogen/progestin Replacement Study in 2000 (22) and WHI estrogen-plus-progestin results in 2002 (7)] that documented harm associated with use of menopausal hormone therapy for chronic disease prevention. Increased cessation of estrogen-plus-progestin use would be expected to produce immediate effects on breast cancer incidence because the increased breast cancer risk associated with estrogen plus progestin is a late-stage effect: breast cancer risk is higher in current users but rapidly declines after cessation of use (5) and returns to the level in nonusers within 5 years. The larger rate increase in the 1990s in the younger versus older women is also consistent with the more frequent use of estrogen plus progestin by younger women and with the higher risks associated with this formulation versus unopposed estrogen (6).

Our incidence data for 2002–2004, (age-adjusted annual incidence rates of 137.0 per 100 000 for 2002–2003 and 123.6 per 100 000 for 2003–2004) are nearly identical to the observed nationwide decline reported by the recent Annual Report to the Nation on the Status of Cancer, 1975–2003, in which breast cancer incidence peaked in 2001 at an age-adjusted rate of 137.3 and then fell to 133.8 in 2002 and 124.2 in 2003 (23). The –4.3% APC in KPNW data from 2000 to 2006 is identical to the –4.3% APC in SEER data from 2000 to 2003 (23).

The incidence trends by receptor status are provocative. The patterns for ER+ cancers will resemble those for total breast cancer because ER+ cancers currently make up more than 80% of breast cancers diagnosed in women older than 45 years of age. It is also consistent with the likelihood that they contribute disproportionately to the slow-growing tumors that are detected with the introduction of mammography, and their stronger association with menopausal hormone therapy use in studies that find a difference by receptor status (24). The incidence rates of ER+ cancer fell sharply from 122.6 per 100 000 women in 1999–2000 to 99.9 in 2003–2004, rose to 108.1 in 2004–2005, and then fell again to 106.4 in 2005–2006. Although these rate swings might represent chance variation, they warrant continued monitoring. It is possible

that some ER+ tumors in menopausal hormone therapy users were undetected yet invasive, such that cessation of menopausal hormone therapy may have simply retarded their growth and postponed their diagnosis by 1 or 2 years. Alternatively, as noted, the KPNW pharmacy shifted estrogen prescriptions from primarily conjugated equine estrogen to estradiol formulations in 2005. Elevated breast cancer risk has been found with both types of estrogens, but potential risk differences have been the source of unconfirmed (25) speculation (26).

The patterns for ER– tumors are more enigmatic. Their rate did not rise during the period of rapid increase in mammography screening, and indeed substantially declined between 1999 and 2006. We anticipated that screening effects would be more apparent for ER+ tumors, which make up a higher percentage of screening-detected cancers than of interval cancers (27,28). However, we also expected to see some screening effects on ER– incidence rates. The lack of any rise in incidence of ER– tumors during the 1990s (when menopausal hormone therapy use substantially increased), followed by a decline in incidence over 2003–2006 that was even more precipitous than the decline seen for ER+ tumors, is particularly difficult to interpret. ER– cancers are far less common than ER+ cancers at KPNW, and thus, instability in the rate estimates could have obscured patterns. There were no identifiable changes in laboratory procedures at KPNW that would have alone accounted for the increased incidence of ER+ tumors and decreased incidence of ER– tumors, but temporal changes in other unknown risk factors for ER– tumors (29) would limit our ability to evaluate the potential association between mammography screening, menopausal hormone therapy use, and incidence of ER– tumors. Simple shifts from ER-unknown to ER+ or ER– cannot explain the increased incidence of ER+ tumors; between 2000 and 2006, as incidence of both ER+ tumors and ER– tumors declined, the percentage of breast cancers with unknown ER status fell from 4% to less than 1%.

Our study has limitations. Similar to other investigations of the impact of mammography and menopausal hormone therapy on breast cancer incidence rates (30,31), ours is a descriptive study evaluating whether population-based rates, rather than individual-level data, were associated with aggregate measures of mammography screening and menopausal hormone therapy prescribing patterns. Thus, it is possible that changes in other, unmeasured causes could have produced the incidence patterns that we observed. However, credible evidence of dramatic changes in other breast cancer risk factors after 2000 has not been documented. We also analyzed data on dispensed hormone therapy prescriptions. To the extent that women did not comply with the prescriptions, we will have underestimated actual usage. On the other hand, by relying on pharmacy dispensing records, we eliminated errors associated with patient recall and reporting. In the aggregate, potential biases due to misclassified hormone therapy use or mammography screening are likely to be small and non-differential. Other publications hypothesized that lower breast cancer incidence rates nationwide in 2003 and 2004 were correlated with decreased menopausal hormone therapy use in other populations after 2002 (10,32). Our data from the KPNW health plan, where breast cancer incidence rates are almost identical to incidence rates in NCI SEER, show that, in a single, large, study

population, the statistically significant decline in breast cancer incidence rates continued through December 31, 2006. Using hormone therapy dispensing data and mammography screening statistics in the KPNW health plan, we showed that breast cancer incidence rates and hormone therapy prescriptions followed parallel tracks of decline from 1999–2000 through 2006, while mammography screening fell slightly in 1999–2000, stabilized through 2003, and then increased from 2004 through 2006.

In summary, since 1980, time trends in breast cancer incidence, particularly for ER+ tumors, seem consistent with the impact of major changes in patterns of mammography screening and use of menopausal hormone therapy. While incidence rates for women under age 45 years remained stable, the rates for women aged 45–59 years and women aged 60 years or older both rose about 50% from the early 1980s to 2001. This rise seemed to occur in two phases, the first during the 1980s, coinciding with the progressive adoption of screening mammography by 75%–79% of eligible women in the plan, and the second corresponding to increases in menopausal hormone therapy use, particularly combined therapy, throughout the 1990s. The incidence rates for both older age groups dropped dramatically in 2003–2006 in conjunction with a profound decline in menopausal hormone therapy prescriptions. Whereas ER– tumor incidence showed the recent dramatic decline, it did not show the two earlier rises.

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