

REPORTS

Rising Incidence of Breast Cancer: Relationship to Stage and Receptor Status

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We used the population-based tumor registry of Kaiser Permanente in the United States (Portland, OR) to analyze breast cancer incidence from 1960 to 1985. Overall, incidence rose 45% during this period. The largest increases occurred in women 60 years of age or older (74%) and in those 45-59 (36%). The rate in women aged 20-44 has remained essentially unchanged. Localized and regional disease showed similar increases. Review of medical records revealed that only a small portion of this increase was likely to result from increased screening activities. From the increased availability of receptor assays in a large proportion of cases since the mid-1970s, we observed that incidence of estrogen receptor-negative cancers rose 22%-27% between the mid-1970s and the mid-1980s. In contrast, incidence of estrogen receptor-positive tumors increased an average of 131% in the same period, perhaps implicating hormonal factors in the rising incidence of breast cancer. [J Natl Cancer Inst 82:693-696, 1990]

The incidence of breast cancer has been rising steadily in the United States for at least 50 years (1), and few explanations account for the increase.

Data from large, population-based registries (2), while encyclopedic, are limited by the absence of detailed information, which is available only from individual patients' medical records. In addition,

time trends from metropolitan registries are often confounded by major changes in the demographic makeup of the population over time.

We have used data from both a population-based tumor registry and individual medical records to characterize, in greater detail, the changing incidence of breast cancer in the relatively homogeneous population of a large prepaid health care plan.

Subjects and Methods

Cases of Breast Cancer

Our population sample comprised all newly diagnosed primary breast cancers among members of Kaiser Permanente (KP), Portland, OR, from 1960 to 1985. Included were 1,830 women with disease diagnosed and treated primarily at KP and 10 women with disease diagnosed at KP but treated elsewhere.

Histological confirmation of the cancer was obtained in all but four of the 1,840 cases: three were diagnosed on clinical grounds and one by x ray alone. We report here only on the subsample of 1,765 invasive cancers.

All cases of breast cancer were staged by the KP tumor registrars using conventions of the American College of Surgeons and the American Joint Commission on Cancer (3). Registrars used material from the inpatient and outpatient medical records, pathology reports, and tumor board discussions to stage each case. Axillary lymph nodes were considered to be involved only if cancer was present on pathological examination. The staging procedure was routinely audited by physician supervisors of the registry.

For the purposes of this study, we grouped cases into three stages:

Stage 1: localized disease—confined to the breast;

Stage 2: regional disease—involving axillary lymph nodes and/or direct extension beyond the breast; and

Stage 3: distant disease—metastases beyond axillary lymph nodes.

Population Data

Population figures came from data routinely compiled by KP on its members. We calculated incidence rates by applying tumor registry figures to the population at risk: the relevant subgroup of KP for the particular age, sex, and year of interest. We performed age adjustment with the direct method, using 5-year age groups and standardizing to the 1970 standard million—a standardized population against which incidence rates can be compared (see ref. 1, pp. 21 and 701).

Hormone Receptors

From February 1972 until September 1974, specimens for hormone receptor assay from primary breast cancers were analyzed at the Worcester Institute (Worcester, MA) by the sucrose gradient method. Subsequently, all specimens were analyzed for estrogen receptor (ER) by the dextran-coated-charcoal method at the Oregon Health Sciences University (OHSU; Portland, OR).

Quantitative results from these two laboratories are used in this study. For this paper, we have considered a receptor

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Table 1. Breast cancer incidence by age and period of diagnosis*

Period of diagnosis	Age-adjusted rate/100,000 population \pm SD for age groups			
	20-44 yr	45-59 yr	\geq 60 yr	All ages
1960-1964	36.1 \pm 8.5 (18)	164.2 \pm 25.0 (43)	214.8 \pm 5.5 (34)	69.2 \pm 7.4 (95)
1965-1969	36.8 \pm 6.7 (30)	166.1 \pm 40.4 (73)	303.4 \pm 9.2 (88)	81.6 \pm 6.2 (191)
1970-1974	36.7 \pm 5.4 (48)	169.0 \pm 45.9 (108)	284.2 \pm 11.0 (127)	79.3 \pm 4.8 (283)
1975-1979	40.4 \pm 4.8 (75)	217.5 \pm 51.8 (156)	287.7 \pm 11.8 (164)	89.2 \pm 4.5 (395)
1980-1985	34.4 \pm 3.3 (118)	221.5 \pm 72.8 (236)	374.6 \pm 12.4 (447)	100.3 \pm 3.6 (801)

* Values in parentheses = No. of cases.

value as negative (ER-) at levels less than 10 fmol/mg of cytosol protein and positive (ER+) at values of 10 fmol/mg and above.

The dividing point of 10 fmol/mg between negative and positive receptor values should have been unaffected by modifications introduced to improve quantification of specimens particularly rich in receptors (Keenan EF: personal communication). The OHSU laboratory participated in quality-control programs of clinical cooperative groups and was repeatedly tested and certified.

Results

The overall age-adjusted annual rate of invasive breast cancer rose 45%, from 69.2 to 100.3/100,000 population, in the period between 1960-1964 and 1980-1985 (table 1). This rate varied by age; the greatest rise occurred in women 60 years of age or older (74%), and an intermediate increase was observed in women 45-59 (36%). There was no consistent rise in incidence among women aged 20-44 during this period.

Increases in incidence for women aged 45-59 were sharp between 1970-1974 and 1975-1979 and much smaller during other intervals. Similarly, for women 60 or older, the increase came in two sharp rises between the first and second periods of observation (1960-1964 and 1965-1969) and between the periods 1975-1979 and 1980-1985.

While such variation could be caused by small numbers of cases in some age categories, these data could also indicate differing risks for different birth cohorts as they pass through the breast cancer age range over the period of observation.

Over the 26 years of observation, the stage at diagnosis of new cases of breast cancer has changed only slightly. Between

1960-1964 and 1965-1969, the proportion of cases diagnosed in a localized disease stage increased from 50% to 58%. This increase was coupled with a complementary decrease in the diagnosis of regional disease from 42% to 32%. Since that time, localized breast cancer has represented 54%-58%, and regional disease 31%-34%, of all newly diagnosed cases. Cases diagnosed as distant disease remained a minor fraction (5%-7%) of all new cases.

By concentrating on the time since

1965, which is the period of more stable proportions of disease at various stages, we can better appreciate the changes in breast cancer incidence by stage at diagnosis (fig. 1). For invasive cancer, localized disease rose 25% between 1965-1969 and 1980-1985. During this same period, regional cancers increased 21%. Incidences of distant disease represented a small fraction of the cases, but its incidence briefly rose in the years 1970-1979, then returned to the 1960-1964 level during the most recent period of observation.

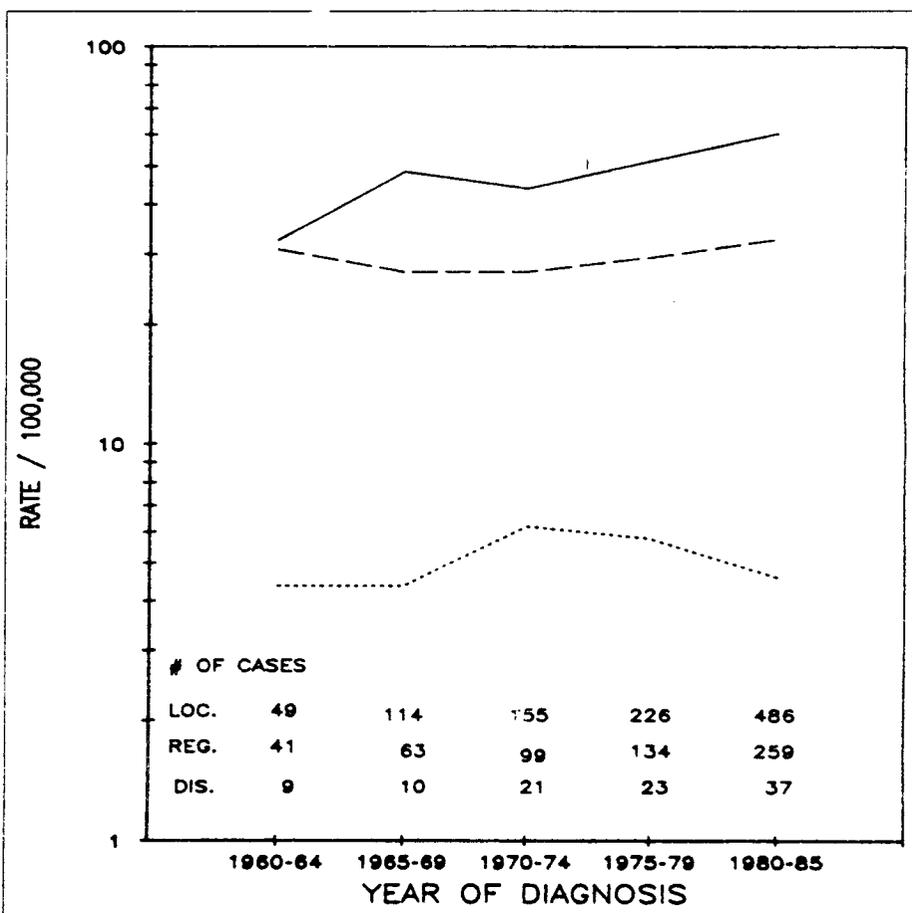


Figure 1. Age-adjusted breast cancer incidence by calendar periods and stage at diagnosis. LOC = localized disease (—), REG = regional disease (---), DIS = distant disease (· · · · ·).

There have been indications that much of the increase in breast cancer incidence may simply result from increased detection due to mammographic screening activities. Because mammographic screening was used little before the 1970s, screening activities are unlikely to explain any increase during that period. Thus, we focused our attention on three intervals from 1972 through 1985. In the period 1972-1976, the age-adjusted rate for invasive breast cancer was 87.0/100,000 population; it rose to 91.6 in the period 1977-1981 and then to 100.3 in the period 1982-1985, resulting in an overall increase of 15.3%.

We reviewed the medical records of women with disease diagnosed in 1972, 1979, or 1985, paying particular attention to events surrounding the time of diagnosis. No woman with disease diagnosed in 1972 or 1979 and only 16 of 178 (9%) with diagnosis in 1985 had breast cancer first detected by a screening mammogram.

Screening activities primarily inflate rates through the dramatic increase associated with the first screening, the "prevalence" examination. In this examination, substantial numbers of lesions present for some time are identified simultaneously. As a result, initial rates for breast cancer are about twice the incidence seen prior to and following the examination. If we assume that all cases identified through screening (9%) resulted from prevalence examinations, then this percentage would have been twice the number expected in the absence of screening. Thus, 4.5% of the rate in the final period might result from screening alone and would account for less than one third of the overall 15.3% increase.

Survival patterns were also investigated (table 2). Over the years of observation, from 1965-1969 to 1980-1985, there was no change in survival for women with localized disease. The rate fluctuated between 80% and 86% at 5 years. For regional disease, survival seems to have improved from 63% to 72% during this period. The small number of deaths resulting from distant disease limited calculation to two periods, 1960-1974 and 1975-1985, and the 5-year survival rate increased from 28% to 41%.

The improvements for regional and distant disease date from 1974-1975, when KP began its active participation in clinical trials of adjuvant treatment of stage 2

Table 2. Survival rate by period of diagnosis and cancer stage

Stage	% survival for period			
	1965-1969	1970-1974	1975-1979	1980-1985
Localized disease	82	86	84	80
Regional disease	63	65	70	72
All stages	72	74	75	73

breast cancer and multimodality therapy for metastatic disease. In contrast, until recently, only a minority of women with localized disease (stage 1) were treated with hormonal therapy or chemotherapy.

In the period 1974-1977, ER assays were performed on 58% of the newly diagnosed breast cancers. Since 1978, ER determinations have been performed in 87% of new cases, and most recently (1984-1986), in 95% of newly diagnosed cancers. We analyzed 1,226 records of invasive breast cancer from the period 1974-1985. Of these cases, 981 had ER determinations and 245 did not; 26 additional cases had ER analysis, but the stage was unknown.

When these values were adjusted for age, there was no major difference in the rate of performance for ER determinations for localized (80%) or regional (84%) disease. Among distant disease cases, 47% had no ER determination, but the number of cases accounted for only 32 women in the entire sample. After adjusting for stage, the rate for performance of ER determinations was comparable (77%-83%) across all age groups. Therefore, failure to perform ER determinations, which occurred in 17%-23% of the cases, was not concentrated in any age group, but the rate was higher for cases of disease already metastatic at diagnosis.

Using population figures for the years 1974-1985, we calculated incidence rates, adjusted to the 1970 standard million, for breast cancers by ER status and stage at diagnosis. Overall, incidence of ER- breast cancer had risen 27%. Per 100,000 population, incidence increased

from 25.4 in 1974-1977 to 31.0 in 1978-1981, and then to 32.3 by 1982-1985. The increase in ER+ tumors during these same periods was 131%, from 24.9 to 39.9 to 57.5/100,000. This rising incidence involved both localized and regional disease to a similar degree. The rise in ER+ cancers with distant disease was larger still, but the number of cases was small and the rates were unstable.

The sharp rise in ER+ cancers occurred only in women older than 45 years of age, and particularly in those 60 or older (table 3). The incidence rose 59% for women 60 or older and 32% for women aged 45-59. The rates for ER- cancers fell 27% in women 45-59 and rose 37% in those 60 or older. Because of the high degree of correlation between age and ER status, residual confounding could be a concern. However, for each 5-year age group from 30-34 to 80-84, the rise in rate of ER- tumors from 1974-1977 to 1982-1985 ranged from 31% to 79%.

Discussion

The rate of invasive breast cancer has increased 45% in the 26 years of observation between 1960 and 1985. Despite this rather remarkable rise and other reports of similar findings (1,4,5), little attention has been paid to this phenomenon. The rise has been consistent and insidious at 1%-2% year, and it has persisted over several decades. Because of the frequency and mortality of breast cancer, the reasons for this increase need to be identified and

Table 3. Breast cancer incidence by age and period of diagnosis for ER+ cancers

Period of diagnosis	Age-adjusted rates: 100,000 population for age groups		
	20-44 yr	45-59 yr	≥60 yr
1978-1981	12.7	83.9	157.3
1982-1985	12.8	111.0	249.3

examined from the public health standpoint.

The greatest increases have occurred in women 60 years of age or older, while there has been no increase for women aged 20–44. After values were adjusted for age, the incidence of cancers rich in estrogen receptors rose much faster than that of cancers that were receptor poor. For the most part, the incidences of localized and regional breast cancers have increased at a similar rate. In addition, there have been no major changes in the stage at diagnosis of breast cancer during the last 20 years.

Speculation that much of the increased incidence of breast cancer could be attributed to detection by mammographic screening or to greater use of routine physical examinations is not supported by our data. Cases detected by mammography screening were a factor only in the most recent period. Even under some extreme assumptions, these cases could have only accounted for less than one third of the increase seen from the mid-1970s to the mid-1980s. Further, the treatment-related, modest improvements in survival for women with regional and distant disease, along with the stability of survival for localized disease and all stages together, indicate that cancers diagnosed more recently were as significant as those seen in earlier years.

A possible explanation of increases in incidence over time might be changing breast cancer risk profiles, particularly those related to fertility of successive birth cohorts. Rises in breast cancer incidence, however, have occurred in each successive birth cohort in the KP Tumor Registry and in the Connecticut Tumor Registry

(6,7), while changes in fertility have fluctuated widely over the last century.

The increase in breast cancer is unlikely to be due to an artifact of cancer registration. Because of the nature of their insurance coverage, KP members may occasionally receive medical care from community physicians. However, care of chronic disease, particularly cancer, occurs almost exclusively in KP facilities. In addition, comparisons of KP data with those of the Connecticut Tumor Registry reveal a close correspondence in rates for those years (1960–1979) for which figures from both registries are available. The KP age-adjusted rates per 100,000 population during this period were 69.2, 81.6, 79.3, and 89.2. The comparable Connecticut figures (1) were 72.8, 80.4, 88.1, and 91.2. The KP rate for 1980–1985 (100.3/100,000) extends this rise to the most recent calendar period.

Perhaps the most provocative aspect of this investigation is the evidence (a) that the rise in breast cancer incidence is most marked for women with ER+ cancers, especially those 60 years of age or older at diagnosis and (b) that this accounts for a large fraction of the total increase in incidence observed. If ER+ and ER– cancers have different etiologic factors, hormonal influences could be responsible for the differential rise in ER+ breast cancer over time.

Our findings are interesting from an etiologic point of view, but they may also have major implications for planning of future therapeutic trials. The nature of breast cancer may be changing in a fundamental way. The incidence in older women is increasing, and their cancers are

more likely to be ER+. Such cancers carry a generally better prognosis, since they tend to grow more slowly and are sensitive to hormonal manipulation. With such major changes occurring in the incidence of breast cancer, one must be cautious when commenting on improving mortality statistics (4,8). The data do not show non-treatment-related improvements in survival, but over the last few years, there has been a marked trend toward a type of breast cancer with better prognosis. Thus, we may see future improvements in mortality rates just from inclusion of a greater number of women with less virulent disease.

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