Twenty-Year Follow-up of the Breast Cancers Diagnosed During the Breast Cancer Detection Demonstration Project

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Abstract

This study reports on the 20-year follow-up of the women diagnosed with breast cancer in the Breast Cancer Detection Demonstration Project (BCDDP) between 1973 and 1980. This project provided 5 years of screening with physical examination and two-view mammography for 280,000 volunteer women across the United States. Based on a 96% follow-up from 1993 to 1995 of the 4,051 women with breast cancer available for analysis, 2,658 (66%) were alive and 1,393 (34%) were dead. A high proportion of the cancers were detected by mammography alone, and 28.6% of all the cancers were smaller than 1.0 cm. Survival rates were calculated by life table method with deaths from breast cancer as the outcome. The adjusted survival rate for the entire group was 80.5%, and the observed survival rate was 61.7%. Adjusted and observed survival rates were 97.2% and 78.5%, respectively, for women with noninvasive cancers and 78.2% and 59.3%, respectively, for those with invasive cancers. Lymph node status and the size of the cancer at diagnosis were prognostic indicators of survival in the BCDDP. Women with invasive cancers and negative lymph nodes had an 85.5% breast cancer survival rate and a 65.6% observed survival rate. Adjusted survival rates for women with invasive breast cancers were 90.2% for cancers smaller than 1 cm, 80.5% for cancers 1.0 to 1.9 cm, 70.5% for cancers 2.0 to 4.9 cm, and 60.6% for cancers larger than 5 cm. Women 40 to 49 years of age demonstrated a greater survival with noninvasive or invasive cancers smaller than 5.0 cm compared with women 50 to 59 and 60 to 69 years of age at diagnosis. These results from the BCDDP are discussed in the context of the recent decline in breast cancer incidence and mortality in the United States.

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Introduction

The present study reports on the 20-year follow-up of the 4,275 women diagnosed with breast cancer between 1973 and 1980 during their participation in the Breast Cancer Detection Demonstration Project (BCDDP). The BCDDP was originally sponsored by the American Cancer Society (ACS) and the National Cancer Institute (NCI). The BCDDP enrolled 283,222 volunteer women 35 to 74 years of age at 29 centers across the United States. Approximately 93,471 women were aged 40 to 49 years, 83,514 were 50 to 59, and 39,471 were 60 to 69. The screening program consisted of five annual screenings using both physical examinations and two-view mammography.[1,2]

The BCDDP was initiated as a demonstration project after the reports in the late 1960s and early 1970s of a 30% decrease in breast cancer mortality in the randomized Health Insurance Program of Greater New York (HIP) study.[3] Other than the expansion in age range from 40 to 64 in the HIP study to 35 to 74 in the BCDDP, the screening protocol in the BCDDP was identical to that offered to women who were randomized to screening in the HIP study. However, there had been substantial improvement in equipment and recording media since the inception of the HIP study. Dedicated mammography machines were introduced in 1969, xeroradiography in 1971, and screen-film systems in 1972.

Twenty-two of the 27 BCDDP centers used xeroradiography exclusively and four used screen film. One center used both. Because of the xeroradiographic characteristics of broad area contrast and edge enhancement, the technique was particularly suited for examination of the dense breast. The large size of the xerographic cassettes also permitted inclusion of the tail of the breast and axilla, resulting in a projection similar to the mediolateral oblique view considered mandatory today but not in general use until the mid-1980s. These improvements in mammography technique[4] resulted in diagnosis of much earlier cancers across all age groups.[5-7]

The importance of the 14-year follow-up (reported in 1993[5] and 1994[6,7]) and now the 20-year follow-up of the women with breast cancer diagnosed in the BCDDP is in the long-term survival data available on women with small breast cancers and in its internal comparisons across age groups. This study, which has a 96% follow-up rate, adds 5.7 years of additional follow-up.

Breast cancer survival patterns were similar across age groups with respect to prognostic factors; however, younger women with in situ and small invasive cancers had slightly increased survival rates.

Methods

The Divisions of Cancer Etiology and Cancer Prevention and Control of the NCI have conducted the follow-up of specific groups of women from the BCDDP to study the risk factors associ-

ated with cancer incidence and death rates. The method used in these follow-up studies has been previously reported.[6] Since the previous report an additional follow-up cycle has been completed (1993 to 1995).

In 1993 all breast cancer cases were matched against the National Death Index. Questionnaires were sent to all women not known to be dead. Nonrespondents received repeated mailings and follow-up by telephone calling as in previous cycles. Throughout the follow-up cycle a major effort was made to determine the vital status of every individual; 164 women were untraceable. Death certificates to determine the cause of death were requested on all deaths and were obtained on all but 66. The 66 deaths without death certificates were fairly evenly divided over age and stage groups. In order not to artificially report a more favorable breast cancer survival rate, for survival analyses this study considered these deaths as deaths from breast cancer, bringing the number of deaths from breast cancer to 777. Adding the deaths without death certificates to the analysis reduced the breast cancer survival rate by 1.5%.

In this analysis, the original group of 4,275 breast cancer cases was reduced by the following exclusions: no available documentation of breast cancer diagnosis for 26 women, 183 women reported a prior diagnosis of breast cancer before entry into the BCDDP, and 15 women had invalid dates of diagnosis or birth, leaving 4,051 women available for analysis.[6] These women were diagnosed as having breast cancer during the BCDDP active screening period of 1973 to 1980. With the most recent follow-up period being from 1993 to 1995, the shortest possible follow-up time was 13 years, the longest was 22 years, and the average was 17.4 years. The follow-up rate was 96% and 164 women (4%) were untraceable.

Mean time from entry to diagnosis and from diagnosis to date of last follow-up or death is expressed in years. Presenting mean time by age at entry and age at diagnosis provided a method to illustrate differences between younger and older women entering or being diagnosed with breast cancer. The time between entry and diagnosis is limited by having only 5 years of active screening. In younger women, the mean time between entry and diagnosis was biased by the cessation of routine mammographic screening after May 1977 in women younger than 50 years who were not at high risk. The mean time between diagnosis and date of last contact or death is influenced by higher comorbidity in the older age groups.

Different methods for evaluating breast cancer survival in the BCDDP were considered. Use of relative survival rates in the BCDDP was problematic because it requires determination of normal life expectancy. Breast cancer survival rates were calculated by life-table survival methods. Only deaths caused by breast cancer were considered events; other individuals were censored from the analysis at the time of their death or their last known follow-up. Using death from breast cancer as the end point, adjusted survival rates[8] adjust for deaths from other causes and allow for comparisons among age groups. It appeared to be the most appropriate measurement of outcome for this study and is less affected by age and comorbidity. (In comparing the differences between relative and adjusted survivals, 52,339 breast cancers diagnosed from 1973 to 1980 in the Surveillance Epidemiology and End Results (SEER) program resulted in a 20-year 53% relative survival rate compared with 57% using the adjusted method based on death certificates).

Previous reports on the BCDDP started with the screening data contained on 17 data tapes, which had as many as four different versions of a single reporting form, all of which had to be resolved by each set of authors. Findings from the early screening program have been previously described by Beahrs et al[1] and Baker et al.[2] Morrison et al[9] attempted to measure the possible mortality benefits, and Seidman et al[10] reported on the 10-year survival rates compared with data in the SEER program of the NCI.

Recently, Smart et al[5] and Byrne et al[6] reported on the 14-year follow-up,

Table 1
BCDDP 20-Year Follow-up Status of Study Cohort

Year	Entry	Diagnosis	Last Alive	Dead
1973	306	102	0	
1974	1,443	538	0	4
1975	1,857	1,025	0	13
1976	445	871	0	27
1977		609	0	38
1978		552	2	82
1979		270	1	91
1980		84	1	89
1981			0	102
1982			2	95
1983			5	93
1984			51	82
1985			33	72
1986			0	66
1987			3	63
1988			52	73
1989			14	65
1990			0	70
1991			0	79
1992			57	65
1993			564	81
1994			1,697	42
1995			176	1
TOTAL	4,051	4,051	2,658	1,393

Table 2
Study of Lapse Years

By Age	Entry to Diagnosis*		Diagnosis to Last Contact†		Diagnosis to Death from BrCa‡	
	No.	Yrs/Case	No.	Yrs/Case	No.	Yrs/Case
35–39	251	1.75	106	14.42	28	6.00
40–44	456	1.76	408	15.34	60	6.32
45–49	795	1.51	687	15.18	103	6.61
50–54	784	1.47	851	14.63	149	6.20
55–59	695	1.46	726	14.42	142	7.11
60–64	520	1.38	592	13.58	122	7.07
65–69	340	1.45	388	13.91	62	6.61
70–74	152	1.25	235	12.12	33	6.91
TOTAL	3,993	1.50	3,993	14.31	711	6.70

* Age at entry of detected cancers; all other tables in this article deal only with age at diagnosis.
† Age at diagnosis of breast cancer.
‡ Age at death from breast cancer (Br Ca).
Note: of the original cohort of 4,051, 58 were either younger than 35 or older than 74.

each with slightly different numbers derived separately from data tapes. The latter report used the Information Management Systems (IMS) group under contract to the NCI for the preparation of the data file. Working with the IMS programmers, the lead investigator of that study derived several variables: age from date of birth to the date of diagnosis, type and size of cancers, and lymph node involvement. These revisions resulted in slight changes in the age-specific frequencies and survival rates between the two reports but did not alter the fundamental findings or conclusions.[5,6] For example, for women aged 40 to 49 years, additional validation changed the 14-year survival among those with in situ cancer from 99.4% to 99.3%, among those with invasive cancer from 81.8% to 83.4%, and so forth.[5,6]

This report updates the Byrne file[6] with the 1993 to 1995 follow-up information. Breast cancers were staged according to the scheme for breast cancer in the fourth edition of the American Joint Committee on Cancer (AJCC) Manual for Staging of Cancer.[8]

Results

In the BCDDP breast cancer cohort of 4,051 women 2,658 (66%) were alive at last contact and 1,393 (34%) were dead (Table 1). Death certificates were obtained on 95.3% of all deaths, providing information on cause of death; 54% (711) were caused by breast cancer. The mean times from entry to diagnosis,

Table 3
20-Year Follow-up of Breast Cancers Diagnosed in the BCDDP by Age Group, Type, Lymph Node Status, Size, Stage, and Modality

	40–49		50–59		60–69		Totals	
TOTAL	1,097		1,577		980		3,654	
TYPE	No.	%	No.	%	No.	%	No.	%
In situ	136	12.4	183	11.6	100	10.2	419	11.5
Invasive*	843	76.8	1,228	77.9	771	78.7	2,842	77.8
Nodes (-)	477	56.6	734	59.8	486	63.0	1,697	59.7
Nodes (+)	362	42.9	477	38.8	276	35.8	1,115	39.2
Nodes (?)	4	0.5	17	1.4	9	1.2	30	1.1
Unknown	118	10.8	166	10.5	109	11.1	393	10.8
SIZE								
T0 (in situ)	136	16.6	183	15.2	100	13.0	419	15.0
T1a+b (0.1–0.9)	104	12.7	153	12.7	123	16.0	380	13.6
T1c (1.0–1.9)	265	32.3	426	35.4	295	38.3	986	35.3
T2 (2.0–4.9)	251	30.6	347	28.8	188	24.4	786	28.1
T3 (> 5.0)	65	7.9	96	8.0	64	8.3	225	8.0
Unknown*	276		372		210		858	
STAGE								
0	136	12.4	183	11.6	100	10.2	419	11.5
I	231	21.1	374	23.7	282	28.8	887	24.3
I (a+b)	63	5.7	100	6.3	87	8.9	250	6.8
I (c)	168	15.3	274	17.4	195	19.9	637	17.4
II	420	38.3	598	37.9	357	36.4	1,375	37.6
II (a+b)	163	14.9	241	15.3	150	15.3	554	15.2
II (c+d)	257	23.4	357	22.6	207	21.1	821	22.5
III	32	2.9	37	2.3	22	2.2	91	2.5
Unknown	278	25.3	385	24.4	219	22.3	882	24.1
MODALITY‡								
PE	56	10.8	40	5.2	24	4.7	120	6.7
MM	227	43.7	379	49.6	279	54.7	885	49.4
Both	236	45.5	345	45.2	207	40.6	788	43.9

* Those of unknown size were not included in the percentage calculations of size (23% of the total).
† The percentage of positive nodes (+) and negative nodes (-) should be to the denominator of invasive cancers.
‡ Only cases detected before May 1977 were included because routine mammography was discontinued in women younger than 50 years after this time.
MM = two-view mammography; PE = physical examination. Note: Age is age at diagnosis.

Table 4
20-Year Adjusted Survival Rates (%) for Women Diagnosed with Breast Cancer in the BCDDP by Age Group, Type, Lymph Node Status, Size, Stage, and Modality

	40–49	50–59	60–69	Totals
TOTAL	**81.2**	**77.6**	**76.0**	**78.3**
TYPE				
In situ	98.2	95.3	93.9	95.8
Invasive	79.4	75.1	74.1	75.8
Node negative	85.1	83.0	81.0	82.9
Node positive	73.4	65.2	63.2	66.8
Unknown	74.7	75.3	72.2	74.3
SIZE (cm)				
T0 (in situ)	98.2	95.3	93.9	95.8
T1a+b (0.1–0.9)	93.6	86.5	85.4	88.1
T1c (1.0–1.9)	80.5	76.5	79.4	78.4
T2 (2.0–4.9)	71.9	69.5	60.6	68.3
T3 (5.0–9.9)	65.2	65.6	53.8	58.0
STAGE				
In situ	98.2	95.3	93.9	95.8
Stage I	89.8	85.3	86.7	86.8
Stage IIa	74.5	77.7	68.1	75.4
Stage IIb	—	71.3	—	71.7
Stage IIc	75.3	68.4	67.6	70.1
Stage IId	69.0	59.9	49.4	59.6
Stage III	—	—	—	40.3
MODALITY				
PE	85.3	76.1	—	82.4
MM	89.1	84.2	83.0	85.1
Both	77.9	74.0	69.1	74.1

— = Too few cases for survival calculations; MM = two-view mammography; PE = physical examination.

Note: Age is age at diagnosis.

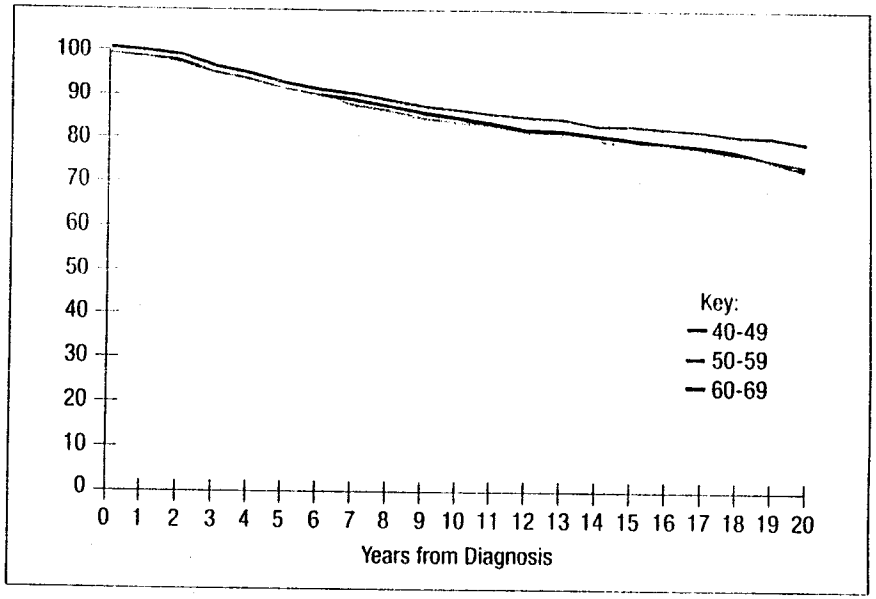

Fig. 1. Breast Cancer Detection Demonstration Project 20-year adjusted survival by age group.

from diagnosis to last contact, and from age at diagnosis until death from breast cancer are shown in Table 2. The mean time from entry to diagnosis ranged from 1.8 to 1.5 years for those younger than 50 years. For those 50 years or older, the lapse time was from 1.3 to 1.5 years. The mean time from entry to diagnosis for the total cohort was 1.5 years. The mean time from diagnosis to last follow-up showed slightly longer times for women 40 to 49 years (15.3 years). Among women who died of breast cancer, the mean time from diagnosis to death was 6.7 years; the time ranged from 6.0 to 6.6 years in women younger than 54 years compared with 6.6 to 7.1 years in women older than 55 years.

Table 3 shows the distribution of cancers by age group, including type of cancer, lymph node status, size, AJCC stage, and mode of detection. Because of the small number of women in the BCDDP younger than 40 years or older than 69 years (397, 10%), these individuals were not included in the age comparisons in Table 3. In the age groups of 40 to 49, 50 to 59, and 60 to 69 there were 1097, 1577, and 980 cases, respectively. Among those women aged 40 to 69, 11.5% of the cancers were in situ, 77.8% were invasive, and 10.8% were unspecified. Because women with cancers in the unspecified category had nearly identical survival compared with those who had invasive cancer, and because among those with known type of cancer 87% were invasive, the majority in the unspecified catagory were probably invasive cancers (Table 4). Considering only the total of 2,812 invasive cancers in which the lymph node status was known, 60.3% had negative lymph nodes and 39.7% had positive lymph nodes. If in situ cancers are also consid-

Table 5
20-Year Adjusted and Observed Survival Rates* of Patients with 4,051 Breast Cancers Diagnosed in the BCDDP

	Adjusted	Observed
In situ	97.2	78.5
Invasive	78.2	59.3
Unknown	79.2	61.4
Nodes negative	85.5	65.6
Nodes positive	68.7	52.6
T1a+b (0.1–0.9)	90.2	70.1
T1c (1.0–1.9)	80.5	60.5
T2 (2.0–4.9)	70.5	54.4
T3 (> 5.0)	60.6	46.9
All ages and types	80.5	61.7

*Survival rates cover ages 35 to 74.

ered node negative, 65.4% of women with breast cancer in which node status was known or with in situ breast cancer had negative lymph nodes.

In 23% of the invasive cancers, size was not recorded; these cancers were not included in the percentages calculated in Table 3. Of those with size information, nearly 50% of the invasive cancers were less than 2.0 cm, and 13.6% were less than 1.0 cm.

Table 3 also shows the distribution of BCDDP cases by AJCC stage. The stage is unknown for 24% of cases because information on tumor size, type (invasive or noninvasive), or lymph node status was not available. Subgroups are also included in general stage distributions. The group aged 40 to 49 comprised 33.5% in stages 0 and I, 38.3% in stage II, and 2.9% in stage III. The distribution of stages at diagnosis was similar across all age groups. Stages Ia and Ib were grouped together to provide sufficient numbers for 20-year survival analyses.

In percentages for the modality of detection, only those detected before May 1977 were included, for comparison purposes. In women aged 40 to 49 years, 43.7% were detected by two-view mammography alone, 45.5% by both two-view mammography and physical examination, and 10.8% by physical examination alone. Thus, 89.2% involved two-view mammography and 56.3% involved physical examination. In women aged 50 to 59 years, 49.6% were detected by two-view mammography alone, 45.2% by both two-

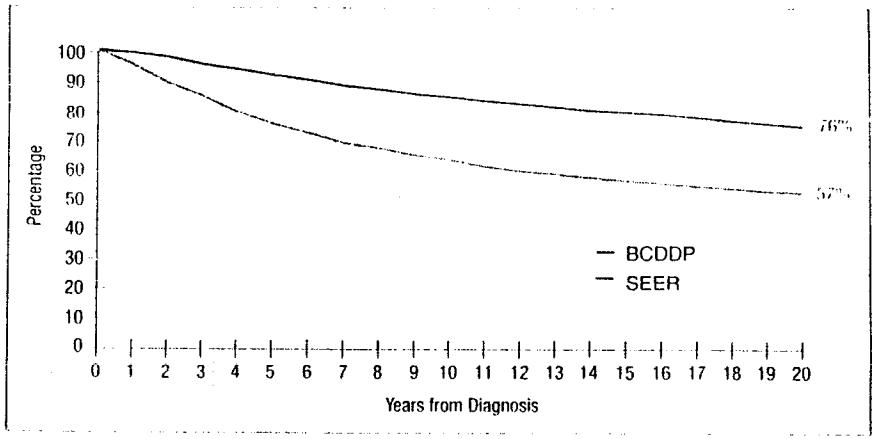

Fig. 2. Twenty-year survival of patients with invasive breast cancer diagnosed from 1973 to 1980 in the Breast Cancer Detection Demonstration Project (BCDDP) and the Surveillance, Epidemiology, and End Results (SEER) program. The SEER program included 52,339 women diagnosed from 1973 to 1980 with a relative survival rate of 53%and an adjusted survival rate of 57%.

view mammography and physical examination, and 5.2% by physical examination alone. Thus, 94.8% involved two-view mammography and 50.4% involved physical examination. The pattern in women 60 to 69 years of age was similar to that of women aged 50 to 59 years.

Table 4 and Fig. 1 compare the 20-year breast cancer survival rates across the age groups 40 to 49, 50 to 59, and 60 to 69. In general, survival patterns were similar across age groups with respect to prognostic factors. However, a slight increase was seen in survival rates for younger women who had in situ cancers, with survival rates of 98.2%, 95.3%, and 93.9%, respectively, for ages 40 to 49, 50 to 59, and 60 to 69 years. Similarly, for invasive cancers (including both those with negative and those with positive lymph nodes), the survival rate decreased with increased age at diagnosis. If the invasive cancers were smaller than 5.0 cm, women aged 40 to 49 years had the highest survival rates. However, for those with breast cancers larger than 5.0 cm, the survival rates were similar for women aged 40 to 49 and 50 to 59 years but substantially lower for women diagnosed at age 60 to 69 years. Among all ages, women with

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favorable tumor characteristics (type, size, and lymph node status) at diagnosis had greater survival rates compared with women with poorer tumor characteristics.

To appreciate the overall results of the BCDDP the entire breast cancer cohort (all ages) of 4,051 cases was analyzed together with a focus on the prognostic factors of type, lymph node status, and size, by both adjusted and observed rates. The entire group of 4,051 cases (including noninvasive cancers) showed an 80.5% breast cancer adjusted survival rate and a 61.7% observed survival rate, as shown at the bottom of Table 5. Those with noninvasive cancers had a 97.2% adjusted cancer survival rate and a 78.5% observed rate, whereas the rates for invasive cancers were 78.2% and 59.3%, respectively. Women who had invasive cancers with negative lymph nodes had an 85.5% adjusted survival rate and a 65.6% observed survival rate. The adjusted survival rates for those with invasive cancers varied with the size of the cancers from 90.2% for cancers smaller than 1 cm, 80.5% for those 1.0 to 1.9 cm, 70.5% for those 2.0 to 4.9 cm, and 60.6% for those larger than 5 cm.

To a great extent the BCDDP has accomplished its purposes: Breast cancer screening has become widespread, the rate of in situ and small invasive cancers has increased dramatically, the rate of advanced cancers has decreased, and breast cancer mortality in the United States has decreased by 6.3%.

Discussion

Breast cancer screening with physical examination and two-view mammography annually for 5 years resulted in the detection of 4,275 breast cancers in the BCDDP. A high proportion of the cancers were detected by mammography alone, and 28.6% of all of the cancers were either in situ or invasive cancers smaller than 1.0 cm (presumably nonpalpable minimal cancers). This is in contrast to the 8% minimal cancers seen in the SEER program over the same time period.

The demographics of the BCDDP and the SEER women with cancer varied greatly. First, SEER is a population-based program that includes all cancer cases, whereas the BCDDP consisted of self-selected volunteers. These volunteers were more highly educated, above average socioeconomically, and both healthy and health conscious; in addition, they were concerned about breast cancer, symptomatic, or at higher risk. In the 10-year survival report on the BCDDP, Seidman found the survival rate for the screen-detected cases was the same as for the interval cases;[10] at the 20-year follow-up our data show the same. These rates may be evidence of the health and breast cancer consciousness of the BCDDP population. Second, in the SEER population mammographic screening was at a low level, whereas in the BCDDP compliance was high, resulting in the detection of a large number of early cancers. In general, demographic factors have not been

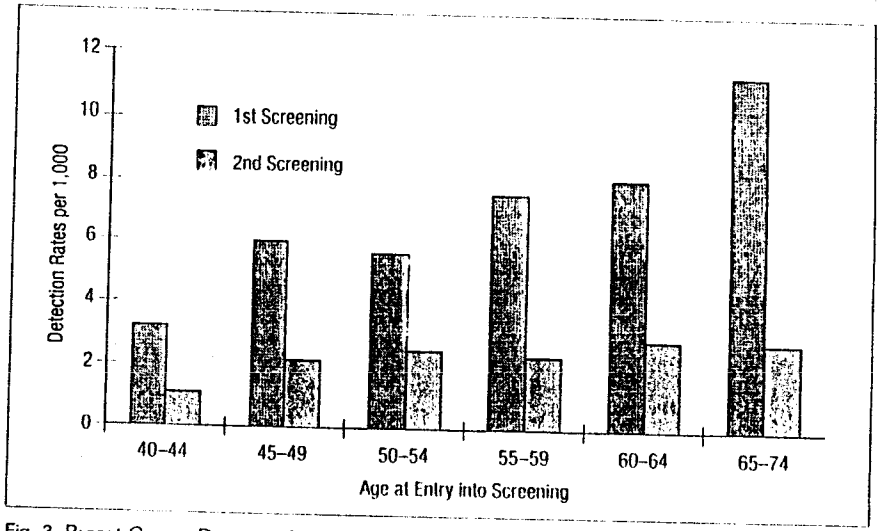

Fig. 3. Breast Cancer Detection Demonstration Project breast cancer detection rates at first and second screenings by age group. Data from Beahrs et al.[1]

strong prognostic indicators of outcome, whereas type, grade, size, and lymph node status (categorized as stage) have been strong indicators.

The 20-year BCDDP breast cancer adjusted survival rate for invasive cancers was 78.2% and the total (observed) survival rate was 59.3% (Table 5). In the United States during the same period of time from the population-based SEER program, 52,339 white women had a 20-year relative survival rate of 53%, an adjusted survival rate of 57% (Fig. 2),[11] and an observed survival rate of 33%.

One of the important factors in the BCDDP was the use of a sensitive screening protocol, annual two-view mammography plus a clinical breast examination. In the controversy over the results of randomized breast cancer screening trials in women 40 to 49 years of age, a delay of 8 to 10 years has usually existed before breast cancer deaths begin to decline in the screened compared with the control groups. Some contended that many women who began screening in their 40s had cancers detected when they were in their 50s and that nearly as much benefit in decreasing mortality could be derived by waiting until age 50 to begin routine mammographic screening. In the BCDDP analyses of the 20-year follow-up of women diagnosed with breast cancers at ages 40 to 49, 50 to 59, and 60 to 69 by modes of detection and type, size, lymph node status, and AJCC stage of cancer, the benefits were similar across age groups.

All women in the BCDDP had the opportunity to have two annual screens before May 1977, when mammographic screening was curtailed in women younger than 50 years. The mean time from entry to diagnosis was slightly longer in younger women. The mean time from diagnosis to outcome was also longer in younger women, partly as a result of slightly higher survival and lower competing comorbidity. However, in the women who died of breast

cancer, the mean time between diagnosis and death was slightly shorter for younger women compared with older women, reflecting the slightly greater proportion of cases in women diagnosed between ages 40 to 49 at stage 2c/d and stage 3 (26.3%, 24.9%, 23.3% for ages 40 to 49, 50 to 59, and 60 to 69, respectively, as seen in Table 3). Despite this slight difference for each level of the prognostic indicators (type, size, and stage) in the women who died of breast cancer, overall survival was slightly greater for younger women.

In the BCDDP the women 40 to 49 years of age had a higher survival rate when their cancers were noninvasive or invasive and less than 5.0 cm compared with women 50 to 59 and 60 to 69. This difference was not present when larger cancers were compared.

The BCDDP was not designed as a trial to evaluate the impact of mammographic screening on survival or mortality and therefore there was no "unscreened" comparison group. In previous analyses, as well as in this longer follow-up, survival in the BCDDP has been compared with the survival experience of white women in the SEER program diagnosed with breast cancer during the same time period.[10]

These inherent limitations have led to attempts to determine if the higher survival in the BCDDP is attributable to the unique characteristics of the study population or to lead time bias caused by detecting cancers at an earlier date without affecting true survival. Although the potential for a lead time bias was an important consideration in the early evaluation of the study, it is unlikely to be an important factor in explaining the magnitude of the survival differences at 20 years. Early analyses of BCDDP data attempted to adjust for lead time in the absence of a comparable comparison group by (1) shifting survival times by a constant value of 1 year or (2) by comparing breast cancer mortality rates in BCDDP participants with expected mortality among women not diagnosed with breast cancer over the same duration.[7,10] In each analysis, BCDDP participants showed a greater survival consistent with both the gain in lead time and early treatment for breast cancer.

Follow-up of cancers detected in the BCDDP shows that women diagnosed with noninvasive cancers have a low breast cancer mortality rate; survival rates for women with invasive cancers relate to the size and lymph node status at the time of diagnosis.

The results of the BCDDP are consistent with the results of randomized clinical trials that showed mortality differences by prognostic factors in women diagnosed by mammographic screening compared with control groups. The BCDDP results also show a similar pattern in survival in premenopausal and postmenopausal women based on tumor size, nodal involvement, and histologic type. Recently, a report of a population-based screening program in Uppsala County, Sweden, showed similar results after 7 years of follow-up.[12] In 56,881 women aged 39 to 71 invited to screening, similar stage distribution and survival rates in women younger and older than age 50 at diagnosis were observed.[12] In fact, similar to what has been observed in the BCDDP, survival was slightly more favorable among younger women than among older women.

This follow-up of the cancers detected in the BCDDP shows that women diagnosed with noninvasive cancers have a low breast cancer mortality rate and that the survival rates for women with invasive cancers relate to the size and lymph node status of the cancer at the time of diagnosis. In 1987, Seidman et al[10] compared the BCDDP and the SEER 10-year survival rates by prognostic factors (including noninvasive and invasive disease by tumor size and lymph node status) and observed similar results if a 1-year lead time was subtracted from the BCDDP data. Now with additional follow-up, lead time should no longer be a major factor and the differences in the overall breast cancer survival rates between the BCDDP and SEER are more reasonably attributed to the shifts in extent of disease at the time of diagnosis.

Because the BCDDP was not a randomized trial, it benefited from high rates of compliance among participants (99% for the first screening and 80% for the second screening); estimates of the benefit of screening were not influenced by the lower compliance rates generally seen in randomized trials for the group invited to screening or from possible contamination in the control group. In the HIP study, only 67% of the study group were actually screened with mammography; although 33% refused, it was necessary to include their death rates from breast cancer with those of women who were screened to avoid bias. Likewise, in most of the breast cancer screening trials since the time of the HIP study, noncompliance has also occurred, and a considerable number of women in the control arm have had mammograms of their own accord. The problems of compliance in the study group and contamination of the control group both are major factors in decreasing the ability to measure reductions in breast cancer deaths and greatly dilute the measurable benefits. Such dilution is not present to the same extent in the BCDDP, in which volunteer compliance was high.

Lower breast cancer incidence in the group aged 40 to 49 years and the higher expense of detecting a single case have been cited as reasons why women in this age group should not be screened.[13,14] In the BCDDP 40% of all the cancers diagnosed were detected in the first screening round. This was true for all age groups: the rate of cancer detection was greatest on the initial screening with mammography. The rate per 1,000 examinations increased with age, reflecting the accumulation of prevalent cases.[1,7] Although the rate of incident breast cancers (diagnosed after first screen) also increased slightly with age, the difference between age-specific rates for incident cases was less than the difference between age-specific rates for the prevalent cases (Fig. 3). The BCDDP shows that the increased screening yield by increasing age is related more to the prevalence (initial) screen than to subsequent screenings. The age-related difference in prevalence cases suggests that many of these cancers accumulated with time, with many more accumulating in older than in younger women because they have lived longer with a cancer detectable by screening. Once these prevalent cancers were screened from the population, however, the detection rate was greatly reduced and was quite similar for all women older than 45 years (2 to 3 per 1,000 examinations). Therefore, on the basis of these data, after a prevalence screening, the cost-effectiveness of subsequent screenings is similar for women aged 45 to 49 years compared

with women older than 50 years.

Conclusions

After the successful HIP study, the BCDDP was designed as a demonstration project to introduce breast cancer screening into the United States for the purpose of reducing breast cancer mortality. To a great extent this project accomplished its purposes; breast cancer screening has become widespread, the rate of in situ and small invasive cancers has increased dramatically, and the rate of advanced cancers has decreased.[15] In November 1996, the ACS, the NCI, and the Centers for Disease Control and Prevention announced a decline in breast cancer mortality rates in the United States.[16] The decrease in mortality for breast cancer in white women was 13% for ages 30 to 39 years, 9% for ages 40 to 49 years, 9% for ages 50 to 59 years, and 6% for ages 60 to 69 years.[16] The decrease was attributed to both earlier detection and improved treatment. The decrease was considerably less for black women, who historically have had less access to screening programs and improved treatment.

The BCDDP as well as some randomized trials have shown that prognostic factors are reliable predictors of outcome.[10,17-22] The indirect evidence based on prognostic factors and 20-year breast cancer adjusted survival data suggest equal benefit in annually screening women with mammography and clinical breast examinations starting at age 40.

Observations from the BCDDP indicate that future evaluation of new procedures for the detection of breast cancer could reasonably consider changes in the distribution rates of the prognostic factors in place of mortality as the end point of the study.

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