Risk of Cardiac Death After Adjuvant Radiotherapy for Breast Cancer

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Background: Women with breast cancer who are treated with adjuvant radiation have a decreased risk of local recurrence but an increased risk of mortality from ischemic heart disease. Patients with left-sided breast tumors receive a higher dose of radiation to the heart than patients with right-sided tumors. Because radiation techniques have improved over time, we investigated whether the risk of death from ischemic heart disease after adjuvant breast radiotherapy decreased over time. Methods: We used the 12-registry 1973–2000 dataset from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program. Women (n = 27,283) treated with adjuvant radiation for breast cancer diagnosed in 1973–1989 were included in the study. Ischemic heart disease mortality was calculated at 15 years and compared for women diagnosed during 1973–1979, 1980–1984, and 1985–1989. Cox proportional hazards models were used to calculate the hazard of death from ischemic heart disease for women diagnosed 1973–1988 and censored at 12 years. All statistical tests were two-sided. Results: There were no differences in age, race/ethnicity, disease stage, or follow-up time between the 13,998 women with left-sided and 13,285 with right-sided cancer. For women diagnosed in 1973–1979, there was a statistically significant difference in 15-year mortality from ischemic heart disease between patients with left-sided (13.1%, 95% confidence interval [CI] = 11.6 to 14.6) and those with right-sided (10.2%, 95% CI = 8.9 to 11.5) breast cancer (P = .02); no such difference was found for women diagnosed in 1980–1984 (9.4%, [95% CI = 8.1 to 10.6] versus 8.7% [95% CI = 7.4 to 10.0]), respectively, P = .64) or 1985–1989 (5.8% [95% CI = 4.8 to 6.8] versus 5.2% [95% CI = 4.4 to 5.9], respectively, P = .98). In the Cox model, the hazard ratio [HR] for ischemic heart disease mortality for women with left-sided versus women with right-sided disease was 1.50 (95% CI = 1.19 to 1.87) in 1979. With each succeeding year after 1979, the hazard of death from ischemic heart disease for women with left-sided versus those with right-sided disease declined by 6% (HR = 0.94, 95% CI = 0.91 to 0.98). Conclusions: Risk of death from ischemic heart disease associated with radiation for breast cancer has substantially decreased over time. [J Natl Cancer Inst 2005;97:419–24]

In the United States in 2002, approximately 42% of women with breast cancer received adjuvant radiation therapy after surgery (1). Adjuvant radiation after breast-conserving surgery decreases the risk of local recurrence by two-thirds and results in survival equivalent to that achieved by patients treated with mastectomy (2,3). Radiation is also recommended for selected patients after mastectomy to lower the risk of recurrence and possibly improve survival (4–8). However, two population-based studies (9,10) have demonstrated underuse of adjuvant radiation therapy, possibly because of concerns about radiation-induced toxicity (9,10). In particular, women treated with radiation have an increased risk of mortality from ischemic heart disease (3,11–15).

In a meta-analysis of eight randomized trials that included almost 8000 women, Cuzick et al. (15) found a 62% increase in cardiac deaths in women who received radiation. Similarly, the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis of approximately 20000 women who were enrolled in 40 randomized trials of radiotherapy found a 30% increase in vascular mortality, although the analysis also documented a statistically significant reduction in breast cancer mortality (3). Because all the trials included in the meta-analysis reported by Cuzick et al. (15) were initiated before 1975 and the trials included in the EBCTCG meta-analysis were also heavily weighted towards trials with patients treated in the 1960s and 1970s, it is unclear whether these data can be applied to women currently undergoing radiotherapy with modern techniques.

Techniques of adjuvant radiation therapy have changed substantially since the 1960s (15–19). Older radiation techniques that resulted in higher doses of cardiac radiation, such as deep tangents and direct internal mammary fields matched to shallow tangents, have been largely abandoned (15–18). In addition, the development of computed tomography-based technology to guide radiation treatment field design has improved the ability to individualize treatment plans. Thus, by accounting for anatomical differences between patients, radiation doses to the heart may be minimized (19). Whether these advances in adjuvant radiotherapy techniques are associated with reduced cardiac mortality has not, however, been rigorously studied.

One approach to study radiation-associated cardiac mortality is to compare outcomes between patients with left-sided breast cancers and those with right-sided breast cancers. Patients with left-sided breast cancer who are treated with radiation have a higher risk of cardiac radiation exposure (13) and higher rates of...
cardiovascular mortality \((11,12,14,20)\) than patients with right-sided breast cancers. The differential dose of cardiac radiation received by patients with left-sided and right-sided breast cancers allows investigators to use observational data to estimate the risk of cardiac mortality from radiation. No known selection biases exist to otherwise differentiate patients by tumor laterality, and an equal distribution of risks would be expected between patients with left- and right-sided tumors. In this study, we compared cardiac mortality rates for patients with left-sided tumors with cardiac mortality rates for those with right-sided tumors to determine whether the risk of death from ischemic heart disease resulting from breast irradiation decreased over time.

**Subjects and Methods**

**Data and Study Population**

Data for this study were obtained from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER)\(^1\) program using the 12-Registry 1973–2000 data set, November 2002 Submission, Released April 2003. In 1973, the SEER network of cancer registries was established and initially included the states of Connecticut, Iowa, Hawaii, New Mexico, and Utah and the metropolitan areas of San Francisco–Oakland and Detroit. In 1974 and 1975, registries in Seattle–Puget Sound and Atlanta were added. In 1992, cancer registries in Los Angeles and San Jose–Monterey and the Alaska Native Tumor registry joined the SEER network to complete the 12 registries used for this study. The case ascertainment rate from the SEER registries has been reported to be 97.5%, and the SEER database is the authoritative source of population-based information on cancer incidence and survival in the United States (21).

The study population included women who were diagnosed with in situ, localized, or regional breast cancer between 1973 and 1989, had known laterality of disease, had surgery for breast cancer, and were treated with radiation therapy. Because information regarding the type of surgery (mastectomy versus breast-conserving surgery) was unavailable before 1983, we did not include the surgical procedure as a variable. We excluded women who had bilateral breast cancer, another primary cancer, or metastatic disease. SEER collects data on radiation therapy that is started within 4 months of diagnosis; thus, women who started radiation after 4 months would not be included in this study. A total of 27,283 women met these criteria.

**Statistical Analysis**

Patients were stratified into three cohorts on the basis of the year of diagnosis: 1973–1979, 1980–1984, and 1985–1989. Within the entire population and within each cohort, patient characteristics were compared between patients with left-sided breast cancers and those with right-sided breast cancers by use of the chi-square test for categorical variables and the t test for continuous variables. Ischemic heart disease mortality rates at 15 years of follow-up were calculated using the Kaplan–Meier estimator for the entire cohort and stratified by stage at diagnosis. Survival rates were compared between women with left- and right-sided breast cancers using the log-rank test. Death from ischemic heart disease was defined by International Classification of Disease (ICD) 9th edition codes of 410–414 or ICD-10 codes of I20–I25, with deaths from other causes censored. Time-to-event curves were calculated using the Kaplan–Meier method for each cohort of patients and stratified by stage at diagnosis.

Cox proportional hazards models were used to calculate the hazard of death from ischemic heart disease. Patients diagnosed between 1973 and 1988 were included in the Cox model \((n = 24785)\). All patients were censored at 12 years of follow-up to ensure equal follow-up. The proportional hazards assumption was checked through a time-dependent covariate presenting the interaction between laterality and follow-up time and by visual inspection of the graph of hazard function for laterality. Because the proportional hazards assumption was violated—that is, the hazards were not proportional over the entire 12 years of follow-up \((P = .03)\)—the time-dependent effect of laterality (up to 8 years and after 8 years) was included in the model. In the first 8 years of follow-up, the ischemic heart disease disease-free survival rates between patients with left-sided cancers and those with right-sided cancers were very similar. The curves for left- and right-sided cancers started to diverge after 8 years of follow-up for patients diagnosed in the 1970s. A piecewise regression model to examine change in left versus right hazard over the period 1973–1988 was fitted at year 1979 because the change in the hazard ratio was not linear over the entire time frame of this study. The choices of 8 years for the follow-up change point and 1979 for the diagnosis year change point were made after examining the data. The final model included age at diagnosis, race/ethnicity, disease stage, time-dependent effect of laterality, and year of diagnosis.

All \(P\) values are two-sided. Statistical analyses were performed using SAS software (Version 8.02, SAS Institute, Cary, NC).

**Results**

Of 27,283 women with early-stage breast cancer who received adjuvant radiation, 13,998 had left-sided breast cancer and 13,285 had right-sided breast cancer (Table 1). Patient age at diagnosis, characteristics of 27,283 women with early-stage breast cancer diagnosed between 1973 and 1989 and treated with adjuvant radiotherapy, stratified by left-sided versus right-sided cancer*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Left-sided cancer</th>
<th>Right-sided cancer</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women</td>
<td>13,998</td>
<td>13,285</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (mean±SD, y)</td>
<td>56.9±13.2</td>
<td>56.8±13.3</td>
<td>.47</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>12,347 (88.2)</td>
<td>11,648 (87.7)</td>
<td>.63</td>
</tr>
<tr>
<td>Black</td>
<td>1017 (7.3)</td>
<td>1006 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>582 (4.2)</td>
<td>582 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>52 (0.4)</td>
<td>49 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1973–1979</td>
<td>4451 (31.8)</td>
<td>4201 (31.6)</td>
<td>.52</td>
</tr>
<tr>
<td>1980–1984</td>
<td>3364 (24.0)</td>
<td>3131 (23.6)</td>
<td></td>
</tr>
<tr>
<td>1985–1989</td>
<td>6183 (44.2)</td>
<td>5953 (44.8)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In situ</td>
<td>460 (3.3)</td>
<td>458 (3.4)</td>
<td>.55</td>
</tr>
<tr>
<td>Localized</td>
<td>6299 (45.0)</td>
<td>5904 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>7239 (51.7)</td>
<td>6923 (52.1)</td>
<td></td>
</tr>
<tr>
<td>Length of follow-up (mean±SD, mo)</td>
<td>111.1±61.0</td>
<td>111.3±61.2</td>
<td>.77</td>
</tr>
</tbody>
</table>

*Patient characteristics by left-sided versus right-sided disease were also compared stratified by the three time-of-diagnosis cohorts (1973–1979, 1980–1984, 1985–1989). There were no statistically significant differences between patients with left-sided and those with right-sided disease in any of the cohorts. \(P\) values were derived by using the chi-square test or \(t\) test, as appropriate. SD = standard deviation.
race/ethnicity, year of diagnosis, stage of disease, and length of follow-up did not differ between women with left-sided and those with right-sided breast cancer.

We examined deaths from ischemic heart disease in women who received radiation for early-stage breast cancer, comparing women with left-sided disease with those with right-sided disease. For the entire study sample, 15-year mortality from ischemic heart disease was higher in women with left-sided breast cancer than in women with right-sided breast cancer (8.7% [95% CI = 6.9% to 9.3%] versus 7.5% [95% CI = 6.9% to 9.2%], respectively), although the difference did not reach statistical significance ($P = .07$). To determine whether the higher ischemic mortality rates in women with left-sided breast cancer were likely associated with radiation, we compared ischemic heart disease mortality at 15 years among women diagnosed 1973 to 1979 who did not receive radiation. In such women there was no difference in ischemic heart disease mortality rates between women with left-sided and those with right-sided disease (10.5% [95% CI = 10.0% to 10.9%] versus 10.9% [95% CI = 10.5% to 11.3%], respectively, $P = .89$).

We next examined differences between women with left-sided and those with right-sided disease stratified by cohorts defined by year of diagnosis. Figure 1 shows the Kaplan–Meier survival curves stratified by laterality and cohort. A decrease in the difference in ischemic heart disease mortality between women with left-sided and those with right-sided disease was seen across the year-of-diagnosis cohorts (Fig. 1). For the 1973–1979 cohort, total ischemic heart disease mortality at 15 years was 13.1% (95% CI = 11.6% to 14.6%) for women with left-sided breast cancer and 10.2% (95% CI = 9.9% to 11.5%) for women with right-sided breast cancer ($P = .02$). For the 1980–1984 cohort, total ischemic heart disease mortality was 9.4% (95% CI = 8.1% to 10.6%) for women with left-sided breast cancer and 8.7% (95% CI = 7.4% to 10.0%) for women with right-sided breast cancer ($P = .64$). For the 1985–1989 cohort, total ischemic heart disease mortality was 5.8% (95% CI = 4.8% to 6.7%) for women with left-sided breast cancer and 5.2% (95% CI = 4.4% to 5.9%) for women with right-sided breast cancer ($P = .98$). The Kaplan–Meier curves also demonstrate that overall cardiovascular mortality declined over the years in the study (Fig. 1).

The percentage of patients with in situ, localized, or regional-stage disease varied with cohort. Among patients diagnosed in 1973–1979, 25.7% had in situ or localized disease and 74.3% had regional disease. Fewer patients were diagnosed with regional-stage disease in the 1980–1984 and 1985–1989 cohorts (51.9% and 35.9%, respectively) than in the 1973–1979 cohort. Therefore, to determine whether the changing stage distribution, and thus likely changing fields of radiation, could account for variation in mortality from ischemic heart disease over time, we generated Kaplan–Meier curves stratified by patient disease stage (Figs. 2 and 3). In patients with in situ or localized disease and in those with regional disease, there was some evidence of a difference in ischemic heart disease mortality between women with left-sided and those with right-sided breast cancer in the 1973–1979 cohort that was not apparent in the 1985–1989 cohort, suggesting that changing stage of disease is unlikely to account for the difference in mortality. Ischemic heart disease mortality rates at 15 years stratified by patient disease stage are shown in Table 2. There was a similar decline over time in the rates of ischemic heart disease mortality between women with left-sided and those with right-sided breast cancer, regardless of the stage of disease.

To further explore the relationship among year of diagnosis, breast cancer laterality, and ischemic heart disease mortality, we constructed Cox proportional hazards models. The models included patients diagnosed between 1973 and 1988; all patients were censored at 12 years of follow-up so that potential follow-up times were identical across the diagnosis years. In these models, the hazard of death from ischemic heart disease was not proportional throughout follow-up, as shown in the Kaplan–Meier curves (Fig. 1). At 8 years or less of follow-up, no statistically significant differences were seen in the hazard of death from ischemic heart disease between women with left-sided breast cancer and those with right-sided breast cancer. At more than 8 years of follow-up, the overall hazard of death from ischemic heart disease ranged from 1.41 to 1.50 for women with left-sided versus right-sided tumors who were diagnosed in the 1970s (e.g., for women diagnosed in 1979, hazard ratio [HR] = 1.50, 95% CI = 1.19 to 1.89).

The primary objective of this study was to determine whether there were changes in risk of death from ischemic heart disease over time. When year of diagnosis was included as a continuous variable, a piecewise Cox model with a break point at 1979 provided the best fit. No change in the hazard of death from ischemic heart disease between women with left-sided breast cancer and those with right-sided breast cancer was seen between 1973 and 1979. For women diagnosed between 1979 and 1988, there was a statistically significant decline in the hazard of death from heart disease between patients with left-sided and those with right-sided breast cancer. For each successive year between 1979 and 1988, the hazard of death from ischemic heart disease for women with left-sided versus right-sided breast cancer decreased by 6% (HR = 0.94, 95% CI = 0.91 to 0.98). For patients diagnosed in
1988, the most recently diagnosed cohort, there was no difference in the hazard of death at 12 years of follow-up between patients with left-sided and those with right-sided breast cancer (HR = 0.79, 95% CI = 0.52 to 1.18). In addition, no interaction was seen between tumor laterality and stage of disease at diagnosis (\( P = .89 \)).

**Discussion**

This population-based analysis revealed that the risk of death from ischemic heart disease among women who received adjuvant radiation for breast cancer decreased over time. As illustrated in the Kaplan–Meier curves (Fig. 1), there was a statistically significant difference in ischemic heart disease mortality between women with left-sided breast cancer and those with right-sided breast cancer in the 1973–1979 cohort that was not apparent in the 1980–1984 and 1985–1989, respectively. Broken lines = patients with left-sided breast cancer; solid lines = patients with right-sided breast cancer; blue lines = 1973–1979 cohort; red lines = 1980–1984 cohort; green lines = 1985–1989.

Beginning in the late 1970s, there was a statistically significant decline in the risk of death from heart disease among women with left-sided versus right-sided tumors. In fact, among women diagnosed in 1988, there was no longer any difference in rates of death from ischemic heart disease between women with left-sided and those with right-sided breast cancers at 12 years.

Our findings are consistent with the considerable progress that has been made in radiation techniques and treatment planning from the 1970s through the late 1980s. The use of orthovoltage radiation, large fraction sizes, and deep tangential fields or direct anterior internal mammary fields to treat the internal mammary lymph nodes, techniques that were common in treatments during the 1970s, has been associated with an increased risk of heart disease (15–18), but these techniques are no longer part of standard practice. Another possible contributor to the decrease in risk of heart disease is the decreasing use of an en face photon or cobalt 60 field to treat the medial chest wall and internal mammary lymph nodes.

Although it is encouraging that adjuvant radiation does not appear to increase the risk of ischemic heart disease mortality for women with breast cancer treated in the late 1980s, the increased risk seen in the women treated in the 1970s adds to the evidence that radiation is potentially cardiotoxic. Therefore, every effort should be made to avoid irradiating cardiac structures. For example, computed tomography (CT)–based treatment planning permits precise imaging of the relationship of the heart to radiotherapy fields. One study estimated that, as a result of the use of modern tangential breast fields and treatment planning, fewer than 5% of patients had heart volumes included in the radiation field that would place them at risk of future cardiac damage (19). Yet, imaging studies have demonstrated perfusion defects that appear within 2 years of adjuvant radiation in approximately 40% of patients, although without any clear clinical sequela (22,23).
Table 2. Comparison of percent ischemic heart disease mortality (with 95% confidence intervals) at 15 years of follow-up between women with left-sided and right-sided breast cancers, stratified by stage of disease at time of diagnosis

<table>
<thead>
<tr>
<th>Cohort by year of diagnosis</th>
<th>All patients</th>
<th>Patients with in situ/localized disease</th>
<th>Patients with regional disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left-sided, %</td>
<td>Right-sided, %</td>
<td><em>P</em></td>
</tr>
<tr>
<td>Overall</td>
<td>8.7 (8.0 to 9.3)</td>
<td>7.5 (6.9 to 8.2)</td>
<td>.07</td>
</tr>
<tr>
<td>1973–1979</td>
<td>13.1 (11.6 to 14.6)</td>
<td>10.2 (8.9 to 11.5)</td>
<td>.02</td>
</tr>
<tr>
<td>1980–1984</td>
<td>9.4 (8.1 to 10.6)</td>
<td>8.7 (7.4 to 10.0)</td>
<td>.64</td>
</tr>
<tr>
<td>1985–1989</td>
<td>5.8 (4.8 to 6.7)</td>
<td>5.2 (4.4 to 5.9)</td>
<td>.98</td>
</tr>
</tbody>
</table>

Small studies of the consequences of modern radiation have not shown any increase in cardiac risk (24–26). The Danish Breast Cancer Cooperative Group 82b and 82c trials of postmastectomy radiation in more than 3000 women treated between 1982 and 1990 showed no increase in risk of ischemic heart disease mortality (HR = 0.84, 95% CI = 0.4 to 1.8) among the women who received radiation (24). Vallis et al. (25) compared the incidence of myocardial infarction in 2128 women treated with breast-conserving surgery and adjuvant radiation therapy between 1982 and 1988. Among 1074 women with left-sided breast cancer, eight experienced fatal myocardial infarction compared with six of 1054 women with right-sided cancer (P = .66). Similarly, Nixon et al. (26) observed no increase in cardiac mortality among 745 patients treated with modern megavoltage techniques. However, none of these studies was powered to detect the 30% to 60% increase in ischemic heart disease mortality found in the earlier meta-analyses (3,15).

Because this study was conducted using observational data rather than data from a randomized trial, we were not able to directly compare patients with and without radiation, nor did we have complete information on all primary therapies. We compared patients with left-sided tumors with patients with right-sided breast cancer because patients with left-sided tumors receive a higher dose of radiation to the heart. All other characteristics of the two groups were similar. Furthermore, all known characteristics, such as patient age and tumor stage, were distributed equally among women with left-sided and right-sided tumors. Although we could have compared women with and without radiation, rather than with left-sided and right-sided tumors, we did not choose the former study design because previous work using the SEER database has shown strong selection biases associated with receipt of adjuvant radiation between women who did and did not receive adjuvant radiation (11). In addition, we were not able to evaluate the relative risks of ischemic heart disease for women who received radiation after mastectomy versus those who received radiation after breast-conserving surgery because the SEER cancer registries did not collect information on type of surgery before 1983. However, in the EBCTCG overview (3), the increased risk of non-breast cancer death after radiotherapy (34% increase) was identical among women treated with mastectomy or breast-conserving therapy. This observation suggests that changing patterns of surgery would not explain the reduction in risk we found over time. In addition, we examined whether there was a relationship with type of surgery for the subset of patients diagnosed between 1983 and 1988, a period when information on type of surgery was available in SEER, and found no difference in the magnitude of the risk associated with radiation after breast-conserving surgery and modified radical mastectomy (P = .69) (data not shown). However, during this period the overall risk of death from ischemic heart disease was low, and therefore our analysis may have been underpowered to detect a small difference.

Another temporal trend that could potentially affect our results is the change in the distribution of cancer stage over time, because patients diagnosed in more recent years had earlier-stage disease than patients diagnosed longer ago. Patients without lymph node involvement (i.e., with early-stage disease) may be less likely to receive radiation to the lymph nodes, especially the internal mammary lymph nodes, and thus could experience less cardiac toxicity. This potential difference in radiation fields by stage of disease could result in a decline in cardiac risk resulting from the trend towards earlier-stage disease. However, when women were stratified by stage, the pattern of decreasing risk from ischemic heart disease mortality over time was similar between the different stages (Figs. 2 and 3). Additionally, we formally tested for an interaction between laterality and stage in the Cox model and found that there was none. This lack of an association suggests that our results are not the result of changing stage distribution.

A potential confounder to these analyses is the length of follow-up. In the proportional hazards analysis, we censored all patients at 12 years to ensure equivalent follow-up. Nevertheless, because of the decline in mortality from breast cancer over time, the mean follow-up was, in fact, longer for women who were diagnosed in the more recent years than it was for women diagnosed earlier. The longer mean follow-up of patients diagnosed in the more recent years would increase the chances of finding any differences in ischemic heart disease mortality between patients with left-sided and those with right-sided cancers diagnosed in the late 1980s. However, we found no difference in ischemic heart disease mortality among these patients, regardless of disease laterality. Because the risk of cardiac mortality from radiation therapy peaks in the second decade after diagnosis (3,20), longer follow-up is needed to estimate the total risk for this study population.

Other potential limitations of this study include death certificate unreliability in cause of death coding (27,28) and possible under-ascertainment of adjuvant radiotherapy by SEER (29,30). However, it does not seem plausible that either of these would introduce directional biases. It is possible that there could be some bias from unobserved risk factors that change over time, although one would not expect a difference by tumor laterality. We are also limited by lack of details on radiation dose, treatment fields, volume of irradiated heart, preexisting cardiac risk factors, and details of treatment including chemotherapy or hormonal therapy use. These limitations are, however, counterbalanced by the advantages of having a large population-based cohort of breast cancer patients with active ascertainment of survival data.

In conclusion, the risk of death from ischemic heart disease associated with radiation therapy for breast cancer has statistically...
significantly decreased over time. These encouraging data suggest that advances in radiation techniques have been translated into substantial benefits for women with breast cancer. Whether the risk of ischemic heart disease mortality resulting from radiotherapy has been entirely eliminated cannot be determined definitively from this study. Continued follow-up of the women diagnosed and treated in the late 1980s will be necessary to answer this question.

### References


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**Notes**

1. Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by 18 nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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