Rates of Myocardial Infarction and Coronary Artery Disease and Risk Factors in Patients Treated With Radiation Therapy for Early-Stage Breast Cancer

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BACKGROUND. Radiation therapy (RT), a critical component of breast-conserving therapy for breast cancer, has been associated with coronary artery disease (CAD) in numerous older studies, but the risk may be lower with modern techniques.

METHODS. Observed rates of cardiac events in 828 patients treated with breast-conserving surgery and RT at the University of Michigan were compared with expected rates. Relations between potential risk factors and actuarial rates of first CAD event were analyzed.

RESULTS. Observed risks of cardiac events were lower than expected. The standardized incidence ratio (SIR) of myocardial infarction (MI) was 0.44 (95% confidence interval [CI]: 0.21–0.70). The SIR of MI or CAD requiring intervention was 0.50 (95% CI: 0.27–0.68). With a median follow-up of 6.8 years, 12 (1.4%) patients had at least 1 MI on follow-up and 20 (2.4%) had at least 1 MI or CAD requiring intervention. Median age at first cardiac event was 75.9 years (range, 43.1–91.5). Median interval from RT to occurrence of the first cardiac event was 3.7 years (range, 13 days to 15.4 years). The 10-year cumulative incidence of MI was 1.2% and cumulative incidence of MI or CAD requiring intervention was 2.7%. On multivariate analysis, age, diabetes mellitus, active smoking, and laterality of RT were significant predictors of MI. Age and active smoking were significant predictors of MI or CAD requiring intervention.

CONCLUSIONS. Patients in this series had lower risk of ischemic cardiac events than expected. Although small in absolute magnitude, patients radiated to the left side did have a statistically significant increased risk of MI. These findings support further investigation of techniques to minimize the long-term cardiac risks faced by breast cancer patients. *Cancer* 2007;109:650–7. © *2007 American Cancer Society.*

KEYWORDS: radiation therapy, breast-conserving therapy, coronary artery disease, cardiotoxicity, breast cancer, myocardial infarction.

Radiation therapy (RT), a critical component of breast-conserving therapy for breast cancer, has been associated with ischemic heart disease in numerous studies.[1–5] Meta-analysis by the Early Breast Cancer Trialists Group indicated that breast cancer patients receiving RT in clinical trials conducted over the past several decades have had significant excess mortality from heart disease (rate ratio 1.27, $P = .0001$).[6] However, caution must be employed when extrapolating the results of this meta-analysis, which included older trials using outdated radiation techniques, to estimate risks for patients treated in the modern era.

Indeed, several single-institution studies have retrospectively compared patients treated to the left and right sides of the chest and failed to document increased risk in series of patients treated with more modern techniques.[7,8] Furthermore, a large population-

based analysis of women treated for breast cancer from 1973–1989 suggested that the increased risk of ischemic heart disease associated with RT has decreased over time.[9] The study, based on data in the Surveillance, Epidemiology, and End-Results (SEER) registries, compared ischemic heart disease mortality in patients with left- vs right-sided radiation treatments, hypothesizing that any difference in risk would be related to the differential cardiac doses received by the 2 groups. In 1979 the hazard ratio for women with left-sided treatment was 1.5, but the hazard of death from ischemic heart disease decreased by 6% with each succeeding year. Moreover, in a separate SEER-based analysis, when investigators compared cardiac morbidity in breast cancer patients treated with adjuvant radiation therapy to the left vs right side from 1986–1993 they found no significant differences in rates of hospitalization for ischemic heart disease, valvular heart disease, conduction abnormalities, or heart failure.[10] Still, it has been noted that even patients treated with RT to the right side may receive some cardiac irradiation if their internal mammary nodes were targeted and, therefore, comparison of patients with left- and right-sided disease may underestimate the potential toxicity of irradiation.[11] Furthermore, potential inaccuracies may exist in the SEER data, particularly regarding the use of radiation therapy, leading some to desire confirmation from more detailed, albeit smaller, databases from single institutions.[12]

A retrospective review of rates of cardiovascular deaths in a population treated with postmastectomy radiation between 1975 and 1994 at a single institution documented very low rates of death from myocardial infarction (MI).[13] Yet in light of another SEER-based study that revealed breast cancer survivors to have a diminished risk of acute MI requiring hospitalization,[14] it is difficult to determine whether the low rate of events in that series simply reflects a lower baseline risk of ischemic cardiac disease in the breast cancer patient population, or whether it truly indicates that radiation therapy administered during that time period had little effect on risk. In fact, cardiac perfusion defects have been documented even in patients treated from 1998–2002 with advanced techniques of 3-dimensional planning,[15] although the clinical consequences of these changes in cardiac perfusion are not yet clear. Moreover, a recent retrospective study of patients treated from 1977 to 1994 at a single institution found a significant increase in posttreatment development of ischemic cardiac disease in left-sided patients, and this series notably included only patients treated with a contemporary tangential irradiation technique.[12] Further research in this area is therefore warranted.

In this study we assessed the incidence of ischemic cardiac events and associated risk factors in a series of patients treated with breast-conserving surgery and RT for early-stage breast cancer at a single institution over the past 2 decades. We also compared rates of ischemic cardiac disease in this population to the rates in an age-, race-, and sex-matched control population.

MATERIALS AND METHODS

From 1984 to 2000, 867 consecutive patients with AJCC 1999 stage I or II breast cancer were treated with breast-conserving surgery and RT at the University of Michigan Hospital.[16] The vast majority of these patients were clinically simulated with fluoroscopic guidance. The University of Michigan began to utilize routine computed tomography (CT)-based planning for all breast cancer patients in February 2000. CT planning, however, was used in node-positive patients from November 1997 onward to incorporate the internal mammary nodes in interspaces 1–3 in the target volume after the publication of the Danish and Canadian postmastectomy radiotherapy trials.[17–19] Megavoltage linear accelerator-generated photon beams were used for treatment.

After obtaining consent from the University of Michigan Institutional Review Board to review patient records for the outlined study, we reviewed these patients' inpatient and outpatient charts and found that 841 of these patients had records sufficient to determine the incidence of ischemic heart disease in follow-up. Patients found on chart review to have received other courses of radiation treatment to the chest for recurrence or other causes were excluded from all analyses. Patients with bilateral breast cancer who received radiation treatment to both sides of the chest were excluded from the comparison of left- vs right-sided patients. Patient demographics were documented, including age and race. Details of the patients' breast cancer treatment were also documented, as well as any systemic therapies received. Adjuvant use of a systemic agent was defined as use of such an agent within 1 year of breast cancer diagnosis.

Charts were reviewed to determine whether patients had any established vascular risk factors at baseline (before their radiation therapy), including hypertension, diabetes, hypercholesterolemia, smoking, history of coronary artery disease (CAD), or history of stroke. Hypertension was established if it was documented in the patient's history, if medications included an antihypertensive agent for which there was no other obvious indication, or if 2 blood pressure readings in excess of 140 systolic or 90 diastolic

were recorded within 1 year of one another, without other explanation. Diabetes was established if listed in the history, if the patient was taking insulin or an oral hypoglycemic agent, or if the laboratory value of hemoglobin A1c exceeded 6.5. Hypercholesterolemia was established if listed in the history, if the patient was taking an antihyperlipidemic agent, if total fasting serum cholesterol exceeded 220, or if fasting LDL exceeded 160. Details of smoking history were recorded, including whether the patient had ever smoked, start and quit dates, pack-years, and whether the patient was actively smoking at the time of RT. History of CAD was also noted, including prior MI, prior percutaneous coronary intervention or bypass surgery, catheterization-documented coronary stenosis, or documented history of angina. History of stroke was also assessed, including prior cerebrovascular accident causing a clinical neurological deficit of longer than 24 hours, infarction noted on brain imaging, or history of transient ischemic attack without persistent neurological deficit.

Charts were also reviewed to establish the development of ischemic heart disease in follow-up. Two categories of cardiac events were defined for analysis. One was restricted to MI alone. The other included either MI or CAD requiring percutaneous intervention or bypass surgery.

Observed rates of cardiac events were compared with expected age-, sex-, and race-specific rates to obtain standardized incidence ratios (SIRs). Expected rates were calculated from the National Hospital Discharge Surveys (NHDS) annual cross-sectional, population-based surveys of hospital discharge events for the US civilian population, obtained from the Centers for Disease Control and Prevention.[20] For purposes of this analysis, NHDS data from 1989 through 2003 were used to calculate the expected rates of cardiac events. For each survey year the NHDS database was queried by relevant ICD-9 diagnostic codes for the outcome of interest. Using the survey weights, the total number of discharges for the particular outcome of interest was calculated and summed across all 15 surveys used. The total discharges were totaled within 5-year age groups, which overlapped with the age distribution for the observed breast cancer patients. Five-year age groups started at age 20–24 and continued through 95–99. The total discharges were also totaled by the race category assigned to the patient (white, black, or other). The civilian population estimates for the US, published by the US Census Bureau,[21] for the survey years were used as the denominator for rate calculations.

The person-years of follow-up in the University of Michigan Radiation Oncology breast cancer database were calculated from the date of initiation of radiotherapy until the patient's date of death or last known contact date (defined strictly by the presence of records adequate to establish whether cardiac events had occurred). For each patient the person-years of follow-up attributed to each 5-year age group were calculated and the total person-years for the study population were summed by race category. The expected number of events for each age group was calculated by multiplying the NHDS rate by the total person-years for each age group. The expected number of events was then summed for all age groups to give an aggregate estimate. The observed to expected ratios—or SIRs—were then calculated. Confidence intervals (CIs) were calculated by iteratively resampling our population with replacement (1000 samples), the bootstrap technique, and calculating the SIR for each sample. Ninety-five percent CIs for the SIR estimates were constructed empirically using the 2.5th and 97.5th percentile of the bootstrap distribution as the confidence limits.[22]

Next, actuarial curves were analyzed to examine the relation between potential risk factors and the actuarial rate of first cardiac event in the patients treated at the University of Michigan. The time to the first cardiac event was calculated from the initiation of radiotherapy. Patients without a cardiac event were censored on the date of their death or last contact.

Relations between potential risk factors and actuarial rate of first cardiac event were analyzed using the product-limit method of Kaplan and Meier and the log-rank test statistic. To develop the best multivariate model for each endpoint, all characteristics were offered simultaneously to a single Cox proportional hazards regression model using a backward elimination algorithm for variable inclusion. Characteristics found to be at least marginally significant ($P < .1$) were retained and compared with bivariate analyses for evidence of confounding. As none was found, final models only retained significant characteristics, with significance defined by the usual P-value less then 5% criterion. Possible 2-way interactions between significant characteristics were also explored.

RESULTS

Of the 867 cases reviewed, 841 patients had medical records sufficient for cardiovascular event follow-up. Of these patients, 7 were excluded from analysis because each of these patients received an additional course of RT to the chest, either before or after treatment of their primary breast cancers, for treatment of other cancers, nonmalignant conditions, or breast cancer recurrence. This left 834 patients analyzable for

TABLE 1
Characteristics of 834 Early-Stage Breast Cancer Patients Treated With Breast-Conserving Surgery and Radiation Therapy at the University of Michigan Hospital From 1984–2000

Characteristic	No.
Age at breast cancer diagnosis, y	
≤35	44
36–50	275
51–65	312
>65	210
Race	
White	771
Black	44
Other	13
Unknown	6
Cardiovascular risk factors	
Hypertension	317
Diabetes mellitus	58
Smoking (ever)	303
Smoking (active)*	164
Hypercholesterolemia	213
Prior stroke	14
Prior coronary artery disease	84
Atrial fibrillation	15
Breast cancer treatment	
Adjuvant tamoxifen[†]	376
Tamoxifen use ever	412
RT laterality	
Left	415
Right	380
Bilateral	39
Adjuvant chemotherapy[†]	326

* Active smoking defined as smoking at the time of radiotherapy (RT) commencement or quit date <2 years before RT commencement.

[†] Adjuvant treatment defined as treatment with a systemic agent within 1 year of breast cancer diagnosis.

FIGURE 1. Cumulative incidence of first posttreatment myocardial infarction following breast-conserving surgery and radiotherapy for breast cancer, stratified by the laterality of the treated breast.

time to first cardiovascular event. The median follow-up time for this population was 6.8 years (range, 1 month to 20.3 years). Excluded cases (n = 33) were similar to the analyzable sample for age, race, and radiation dose administered to the breast. For an additional 6 patients, medical records could not identify the patient's racial group. Therefore, 828 patients, comprising 6232 person-years, were used for comparison to the general population's expected cardiovascular events rates and for calculation of SIRs.

Of the analyzable sample (N = 834), 795 received radiation therapy to 1 breast alone. In the analyses that follow below, results based on the full set of 834 cases are presented where possible. Exceptions include the calculations of SIRs and time-to-event analyses that consider the laterality of the radiotherapy treatment, where 828 and 795 patients are considered, respectively.

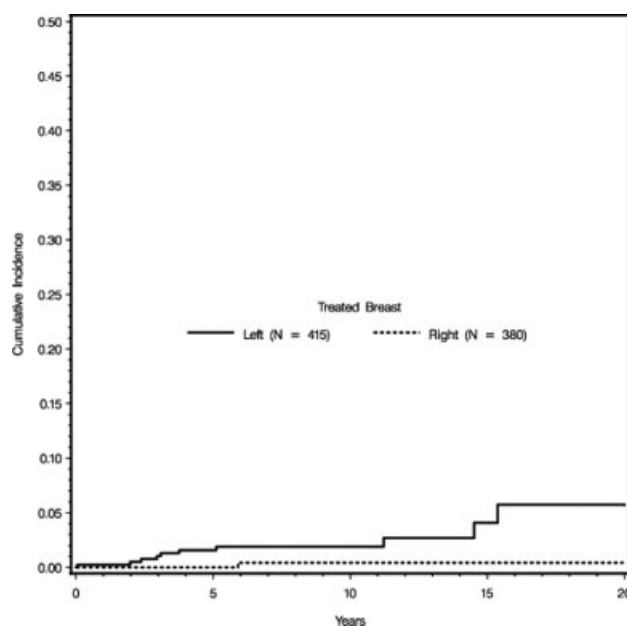Demographic characteristics of the patient population, cardiovascular risk factors, and characteristics of breast cancer treatment are detailed in Table 1. Median patient age at time of RT was 55.7 years (range, 21.7–88.5 years).

Overall, 12 (1.4%) patients had at least 1 MI on follow-up and 20 (2.4%) patients had at least 1 MI or CAD requiring intervention on follow-up. Of the patients with MI, all had a single event. When considering either MI or CAD requiring intervention, and defining "event" as a single episode in terms of time (during which a patient might have had both an MI and an intervention), 18 patients had a single event, 1 had 2 events, and 1 had 3 events.

The median age at first cardiac event (either MI or CAD requiring intervention) was 75.9 years (range, 43.1–91.5). The median interval from initiation of RT to occurrence of the first cardiac event was 3.7 years (range, 13 days to 15.4 years).

The overall risks of cardiac events were lower than those in the age-matched control population. The SIR of MI was 0.44 (95% CI: 0.21–0.70). The SIR of MI or CAD requiring intervention was 0.50 (95% CI: 0.27–0.68).

Figure 1 shows the cumulative incidence of MI and Figure 2 shows the cumulative incidence of cardiac events (either MI or CAD requiring intervention), by laterality, during follow-up for the 795 patients in the University of Michigan series treated with RT to 1 side. At 10 years of follow-up the overall cumulative risk was 1.2% for MI and 2.7% for MI or CAD requiring intervention.
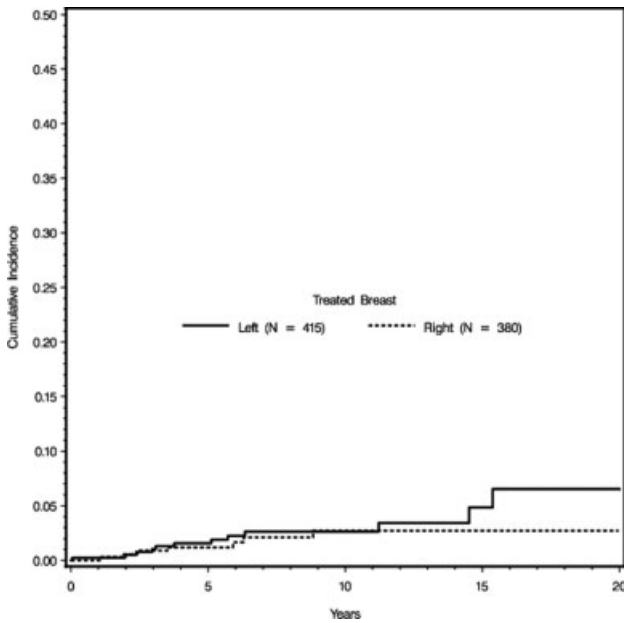
FIGURE 2. Cumulative incidence of first posttreatment myocardial infarction and coronary artery disease requiring intervention following breast-conserving surgery and radiotherapy for breast cancer, stratified by the laterality of the treated breast.

TABLE 2
Hazard Ratios of Various Cardiovascular Risk Factors and Treatment-Related Characteristics for First Cardiac Event, Adjusted for Patient Age at Breast Cancer Treatment

Characteristic	MI alone		MI or CAD requiring intervention	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Hypertension	1.51 (0.43–5.25)	.51	1.21 (0.48–3.07)	.69
Diabetes mellitus	3.84 (1.07–13.78)	.04	2.63 (0.91–7.64)	.07
Smoking, ever	3.28 (1.03–10.44)	.04	1.53 (0.62–3.76)	.36
Smoking, active	5.68 (1.55–20.74)	.009	3.34 (1.15–9.72)	.03
Hypercholesterolemia	0.49 (0.11–2.25)	.36	1.07 (0.41–2.77)	.90
Previous coronary artery disease	2.64 (0.75–9.29)	.13	1.77 (0.62–5.05)	.29
Atrial fibrillation	2.43 (0.30–19.87)	.41	1.39 (0.18–10.63)	.75
Adjuvant tamoxifen	0.80 (0.25–2.58)	.70	0.87 (0.35–2.12)	.75
Tamoxifen use ever	0.70 (0.22–2.24)	.54	0.76 (0.31–1.84)	.54
Left-sided RT*	9.07 (1.16–71.18)	.04	1.56 (0.61–3.98)	.35
Adjuvant Chemotherapy	1.09 (0.21–5.79)	.92	1.36 (0.40–4.62)	.63

MI indicates myocardial infarction; CAD, coronary artery disease; RT, radiotherapy.

* Bilateral cases excluded, leaving a sample size of 795.

The occurrence of first MI was strongly associated with the age of the patient at breast cancer treatment (hazard ratio [HR] = 1.11, 95% CI: 1.05–1.17, P = .0004). The occurrence of first MI or CAD requiring intervention was also strongly associated with the age of the patient at breast cancer treatment

TABLE 3
Best Multivariate Models for First Posttreatment Cardiac Event

Characteristic	First MI*	First MI or Intervention for CAD
Age, continuous	1.12 (1.04–1.20)	1.11 (1.06–1.16)
P	.002	<.001
Diabetes		
Yes vs no	4.42 (1.13–17.31)	
P	.03	
Smoker, active		
Yes vs no	6.95 (1.83–26.33)	3.34 (1.15–9.72)
P	.004	.03
Treated breast		
Left vs right	7.92 (1.01–62.28)	
P	.05	

MI indicates myocardial infarction; CAD, coronary artery disease.

* Bilateral cases were excluded leaving a sample size of 795 cases.

(HR = 1.09, 95% CI: 1.05–1.14, P < .0001). Bivariate associations for other baseline risk factors and clinical and treatment characteristics, after adjustment for the patient's age at breast cancer treatment, are presented in Table 2. There was no significant relation between the incidence of cardiac events and tamoxifen or chemotherapy administration. Factors significantly associated with the cumulative incidence of first MI included diabetes mellitus, smoking, and laterality of the irradiated breast. The only factor significantly associated with the incidence of first MI or CAD requiring intervention was active smoking, although diabetes mellitus also trended toward significance.

On multivariate analysis, as shown in Table 3, age, diabetes mellitus, active smoking, and laterality of the treated breast remained significant predictors of MI. Age and active smoking were the only significant predictors of MI or CAD requiring intervention.

DISCUSSION

Techniques of radiation therapy have evolved dramatically over the past several decades.[23] By the 1980s, most radiation oncologists had abandoned cobalt units and outdated techniques such as deep tangents and en face 'hockey stick' fields and began routinely to treat breast cancer patients with standard tangents with megavoltage linear accelerators. In more recent years, some centers also began to use 3D CT-based planning for left-sided breast cancers.[24] 3D planning may be particularly useful for minimizing cardiac irradiation because it allows for quantification of heart dose and greater planning flexibility to utilize off-axis fields and exploit the angles of treatment based on each patient's unique geometry. However, the use of CT-planning for breast cancer has only slowly become more widespread in clinical practice. Indeed, a recent analysis of patterns

of care in 1998–1999 documented CT planning use in 22.9% of breast cancer cases, compared with 9% in 1993–1994.[25] More recently, even more sophisticated techniques—including intensity modulated radiation therapy,[26] breathing controlled radiation,[27–31] and other innovations[32]—have also been explored.

In this series of patients treated at the University of Michigan over the past 2 decades the overall risks of MI and CAD requiring intervention were significantly lower than the expected rates calculated using the NHDS. Nevertheless, we did find a statistically significant increase in the risk of MI in patients irradiated to the left breast, compared with those irradiated to the right. Given the size of this single institution's series and the small number of events, the size of the confidence interval surrounding the hazard ratio is quite large. Moreover, the absolute risk is extremely low, such that even a large increase in relative risk contributes to an absolute risk elevation that is small in magnitude. Nevertheless, given other studies suggesting that the cardiac toxicity from RT is not fully manifest until many years after exposure,[33] it is noteworthy that this study, with a median follow-up of 7 years, did detect a difference between left- and right-sided treatment. Furthermore, this study is consistent with the experience recently reported by the University of Pennsylvania, where left-sided patients treated with tangential irradiation were again found to have significantly higher rates of chest pain, CAD, and MI.[12]

Therefore, this finding supports further investigation of the potential impact of CT planning in allowing quantification and reduction of cardiac dose, as compared with the clinical planning utilized for the treatment of the vast majority of patients in this study. In light of the data that even patients treated with CT planning may have significant perfusion defects,[15] it is important to obtain long-term clinical follow-up in patients treated with this technique. This is particularly important because the use of chemotherapeutic agents such as doxorubicin and trastuzumab in the modern era may compound any radiation-induced damage that may occur. In addition, it will be valuable to compare these results with those obtained using techniques such as intensity modulation and breathing control, which may be valuable in further minimizing the long-term cardiac risks faced by breast cancer patients, particularly with left-sided disease. Ideally, these clinical outcomes should be assessed in the context of a randomized clinical trial.

Patients in this series had a lower risk of MI and CAD requiring intervention than expected from comparison to a matched control population. This suggests that survivors of early-stage breast cancer may have a lower risk of ischemic cardiac events compared with the general American population. This is consistent with the finding of the only other published study exploring MI rates in breast cancer patients of which we are aware.[13] The mechanisms for this finding have yet to be established, but hypotheses have been proposed.

One possibility is that the use of hormonal therapy in many of these patients may lower their cardiac risk, although the net effects of selective estrogen receptor modulators upon cardiac risk have yet to be clearly established.[34–40] Another possibility is that endogenous estrogens, which play a pathogenetic role in the development of breast cancer, may be protective against cardiac disease. Yet another interesting idea is that IGF-1, which has also been implicated in the pathogenesis of breast cancer,[41] may have vasculoprotective effects.[42–44] Further study is necessary to explore each of these possibilities, which may have important implications for the treatment of both breast cancer and cardiac disease.

However, it is important to note the potential limitations of the comparison of the University of Michigan series to a control population drawn from the NHDS. First, because of a change in the ICD-9 coding system in 1989, only the years 1989–2003 could be used in calculating expected rates, whereas observed rates were drawn from a cohort treated between the years 1984–2000 (and followed through 2004). Therefore, to some extent, a simple increase in the incidence of CAD over time would itself contribute to a finding of a lower rate of CAD in the observed population than expected, insofar as the expected rates were calculated from a population derived from later years. Still, it does not appear that the age-adjusted incidence of CAD has increased in the past 2 decades.[45,46] Furthermore, this study relies heavily on the accuracy of the NHDS sampling strategy and US Census Bureau's yearly population estimates. It is important to note that there was considerable variability from year to year in the mean rates of cardiac events in these surveys, when summed by 5-year age group and race categories, as used to construct the population parameters for our calculations. Therefore, although the strongly significant finding suggests that rates of MI and CAD requiring intervention are likely lower among the patients in our series than expected, the actual magnitude of the difference in observed and expected rates may be overestimated due to these methodological issues in the calculation of expected rates.

Conclusions

In summary, in this series of patients treated for early-stage breast cancer with breast-conserving surgery and adjuvant RT at the University of Michigan,

the cumulative incidence of MI and CAD requiring intervention was very low, and significantly lower than that which would have been expected based on the patients' age, sex, and race alone. There appears to be some increased risk for patients treated to the left side of the chest, compared with those treated to the right, but the absolute magnitude of the increased risk, at least during the first decade after treatment, is low. Nevertheless, these findings support further assessment of clinical outcomes when newer techniques of CT planning are employed, as well as investigation of the potential role of innovative techniques such as intensity modulated radiotherapy and breathing controlled radiation. Such techniques may be valuable in reducing the volume of heart irradiated and, therefore, the long-term mortality and morbidity that may result from this integral part of the conservative treatment of breast cancer, particularly in patients with left-sided disease.

REFERENCES

1. Paszat LF, Mackillop WJ, Groome PA, et al. Mortality from myocardial infarction after adjuvant radiotherapy for breast cancer in the surveillance, epidemiology, and end-results cancer registries. *J Clin Oncol.* 1998;16:2625–2631.
2. Paszat LF, Mackillop WJ, Groome PA, et al. Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: a population-based study in Ontario, Canada. *Int J Radiat Oncol Biol Phys.* 1999;43:755–762.
3. Rutqvist LE, Lax I, Fornander T, et al. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. *Int J Radiat Oncol Biol Phys.* 1992;22:887–896.
4. Rutqvist LE, Johansson H. Mortality by lateralty of the primary tumour among 55000 breast cancer patients from the Swedish Cancer Registry. *Br J Cancer.* 1990;61:866–868.
5. Cuzick J, Stewart H, Rutqvist L, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol.* 1994;12:447–453.
6. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet.* 2000;355:1757–1770.
7. Nixon AJ, Manola J, Gelman R, et al. No long-term increase in cardiac-related mortality after breast-conserving surgery and radiation therapy using modern techniques. *J Clin Oncol.* 1998;16:1374–1379.
8. Vallis KA, Pintilie M, Chong N, et al. Assessment of coronary heart disease morbidity and mortality after radiation therapy for early breast cancer. *J Clin Oncol.* 2002;20:1036–1042.
9. Giordano SH, Kuo YF, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. *J Natl Cancer Inst.* 2005;97:419–424.
10. Patt DA, Goodwin JS, Kuo YF, et al. Cardiac morbidity of adjuvant radiotherapy for breast cancer. *J Clin Oncol.* 2005;23:7475–7482.
11. Prosnitz RG, Marks LB. Radiation-induced heart disease: vigilance is still required. *J Clin Oncol.* 2005;23:7391–7394.
12. Harris EER, Correa C, Hwang WT, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. *J Clin Oncol.* 2006;24:4100–4106.
13. Woodward WA, Strom EA, McNeese MD, et al. Cardiovascular death and second non-breast cancer malignancy after postmastectomy radiation and doxorubicin-based chemotherapy. *Int J Radiat Oncol Biol Phys.* 2003;57:327–335.
14. Lamont EB, Christakis NA, Lauderdale DS. Favorable cardiac risk among elderly breast carcinoma survivors. *Cancer.* 2003;98:2–10.
15. Marks LB, Yu X, Prosnitz RG, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys.* 2005;63:214–223.
16. Pierce LJ, Griffith KA, Hayman JA, et al. Conservative surgery and radiotherapy for stage I/II breast cancer using lung density correction: 10-year and 15-year results. *Int J Radiat Oncol Biol Phys.* 2005;61:1317–1327.
17. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med.* 1997;337:949–955.
18. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet.* 1999;353:1641–1648.
19. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med.* 1997;337:956–962.
20. National Hospital Discharge Survey. Available at URL: http://www.cdc.gov/nchs/about/major/hdasd/nhds.htm
21. United States Census. Available at URL: http://www.census.gov
22. Efron B, Tibshirani RJ. Monographs on Statistics and Applied Probability 57: An Introduction to the Bootstrap. Boca Raton, FL: Chapman & Hall/CRC; 1998.
23. Gyenes G, Gagliardi G, Lax I, Fornander T, Rutqvist LE. Evaluation of irradiated heart volumes in stage I breast cancer patients treated with postoperative adjuvant radiotherapy. *J Clin Oncol.* 1997;15:1348–1353.
24. Das IJ, Cheng EC, Freedman G, Fowble B. Lung and heart dose volume analyses with CT simulator in radiation treatment of breast cancer. *Int J Radiat Oncol Biol Phys.* 1998;42:11–19.
25. Pierce LJ, Moughan J, White J, Winchester DP, Owen J, Wilson JF. 1998–1999 patterns of care study process survey of national practice patterns using breast-conserving surgery and radiotherapy in the management of stage I-II breast cancer. *Int J Radiat Oncol Biol Phys.* 2005;62:183–192.
26. Cho BCJ, Schwartz M, Mijnheer BJ, Bartelink H. Simplified intensity-modulated radiotherapy using pre-defined segments to reduce cardiac complications in left-sided breast cancer. *Radiother Oncol.* 2004;70:231–241.
27. Krauss DJ, Kestin LJ, Raff G, et al. MRI-based volumetric assessment of cardiac anatomy and dose reduction via active breathing control during irradiation for left-sided breast cancer. *Int J Radiat Oncol Biol Phys.* 2005;61:1243–1250.
28. Sixel KE, Aznar MC, Ung YC. Deep inspiration breath hold to reduce irradiated heart volume in breast cancer patients. *Int J Radiat Oncol Biol Phys.* 2001;49:199–204.
29. Pedersen AN, Korreman S, Nystrom H, Specht L. Breathing adapted radiotherapy of breast cancer: reduction of cardiac and pulmonary doses using voluntary inspiration breath-hold. *Radiother Oncol.* 2004;72:53–60.

30. Lu HM, Cash E, Chen MH, et al. Reduction of cardiac volume in left-breast treatment fields by respiratory maneuvers: a CT study. *Int J Radiat Oncol Biol Phys.* 2000;47:895–904.

31. Chen MH, Cash EP, Danias PG, et al. Respiratory maneuvers decrease irradiated cardiac volume in patients with left-sided breast cancer. *J Cardiovasc Magn Reson.* 2002;4:265–271.

32. Gladstone DJ, Flanagan MF, Southworth JB, et al. Radiation-induced cardiomyopathy as a function of radiation beam gating to the cardiac cycle. *Phys Med Biol.* 3004;49:1475–1484.

33. Darby SC, McGale P, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol.* 2005;6:557–565.

34. Rutqvist LE, Matteson A. Cardiac and thromboembolic morbidity among postmenopausal women with early stage breast cancer in a randomized trial of tamoxifen: the Stockholm Breast Cancer Study Group. *J Natl Cancer Inst.* 1993;85:1398–1406.

35. MacDonald CC, Alexander FE, Whyte BW, et al. Cardiac and vascular morbidity in women receiving adjuvant tamoxifen for breast cancer in a randomized trial. *BMJ.* 1995;311:977–980.

36. Constantino JP, Kuller LH, Ives DG, Fisher B, Dignam J. Coronary heart disease mortality and adjuvant tamoxifen therapy. *J Natl Cancer Inst.* 1997;89:776–782.

37. Reis SE, Constantino JP, Wickerham DL, et al. Cardiovascular effects of tamoxifen in women with and without heart disease: breast cancer prevention trial. *J Natl Cancer Inst.* 2001;93:16–21.

38. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women. Four-year results from the MORE (multiple outcomes of raloxifene evaluation) randomized trial. *JAMA.* 2002;287:847–857.

39. Beral V, Banks E, Reeves G. Evidence from randomised trials on the long-term effects of hormone replacement therapy. *Lancet.* 2002;360:942–944.

40. Braithwaite RS, Chlebowski RT, Lau J, et al. Meta-analysis of vascular and neoplastic events associated with tamoxifen. *J Gen Intern Med.* 2003;18:937–947.

41. Moschos SJ, Mantzoros CS. The role of the IGF system in cancer: from basic to clinical studies and clinical applications. *Oncology.* 2002;63:317–333.

42. Conti E, Marchese N, Andreotti F. Correspondence: favorable cardiac risk among elderly breast carcinoma survivors. *Cancer.* 2004;100:878–879.

43. Conti E, Pitocco D, Capuluongo E, et al. IGF-1 and macrovascular complications of diabetes. *Diabetes Care.* 2003;26:1653–1654.

44. Van den Beld AW, Bots ML, Janssen JA, Pols HA, Lamberts SW, Grobbee DE. Endogenous hormones and carotid atherosclerosis in elderly men. *Am J Epidemiol.* 2003;157:25–31.

45. Arciero TJ, Jacobsen SJ, Reeder GS, et al. Temporal trends in the incidence of coronary disease. *Am J Med.* 2004;117:228–233.

46. Goldberg RJ, Yarzebski J, Lessard D, Gore JM. A two-decades (1975 to 1995) long experience in the incidence, in-hospital and long-term case-fatality rates of acute myocardial infarction: a community-wide perspective. *J Am Coll Cardiol.* 1999;33:1533–1539.