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ORIGINAL REPORT

Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials

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ABSTRACT

Purpose

Radiotherapy reduces the absolute risk of breast cancer mortality by a few percentage points in suitable women but can cause a second cancer or heart disease decades later. We estimated the absolute long-term risks of modern breast cancer radiotherapy.

Methods

First, a systematic literature review was performed of lung and heart doses in breast cancer regimens published during 2010 to 2015. Second, individual patient data meta-analyses of 40,781 women randomly assigned to breast cancer radiotherapy versus no radiotherapy in 75 trials yielded rate ratios (RRs) for second primary cancers and cause-specific mortality and excess RRs (ERRs) per Gy for incident lung cancer and cardiac mortality. Smoking status was unavailable. Third, the lung or heart ERRs per Gy in the trials and the 2010 to 2015 doses were combined and applied to current smoker and nonsmoker lung cancer and cardiac mortality rates in population-based data.

Results

Average doses from 647 regimens published during 2010 to 2015 were 5.7 Gy for whole lung and 4.4 Gy for whole heart. The median year of irradiation was 2010 (interquartile range [IQR], 2008 to 2011). Meta-analyses yielded lung cancer incidence ≥ 10 years after radiotherapy RR of 2.10 (95% CI, 1.48 to 2.98; $P < .001$) on the basis of 134 cancers, indicating 0.11 (95% CI, 0.05 to 0.20) ERR per Gy whole-lung dose. For cardiac mortality, RR was 1.30 (95% CI, 1.15 to 1.46; $P < .001$) on the basis of 1,253 cardiac deaths. Detailed analyses indicated 0.04 (95% CI, 0.02 to 0.06) ERR per Gy whole-heart dose. Estimated absolute risks from modern radiotherapy were as follows: lung cancer, approximately 4% for long-term continuing smokers and 0.3% for nonsmokers; and cardiac mortality, approximately 1% for smokers and 0.3% for nonsmokers.

Conclusion

For long-term smokers, the absolute risks of modern radiotherapy may outweigh the benefits, yet for most nonsmokers (and ex-smokers), the benefits of radiotherapy far outweigh the risks. Hence, smoking can determine the net effect of radiotherapy on mortality, but smoking cessation substantially reduces radiotherapy risk.

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INTRODUCTION

Randomized trials show that radiotherapy substantially reduces breast cancer recurrence and moderately reduces absolute breast cancer mortality by a few percentage points, depending on cancer characteristics.[1,2] For suitable patients, these benefits outweigh any long-term risks.[3,4]

Because most women with early breast cancer are cured of their disease, the issue of survivorship is important. Late hazards may be caused by radiotherapy or systemic therapy. Tamoxifen can cause endometrial cancer,[5,6] cytotoxic drugs can cause leukemia,[7] and trastuzumab and anthracyclines can cause cardiac disease.[5,7-9] For breast cancer radiotherapy, the main long-term hazards are second primary lung cancer and heart disease.[8,10]

ASSOCIATED CONTENT

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Data Supplement
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The absolute hazards from modern breast cancer radiotherapy regimens for typical patients depend on the lung and heart doses from modern regimens, the excess rate ratios (ERRs) per Gy for lung cancer and heart disease, and future lung cancer and heart disease mortality rates in the population. Rates of lung cancer and heart disease in the general population depend strongly on smoking. Women who smoke throughout adulthood have approximately 20 times the lung cancer mortality rates and four times the cardiac mortality rates of nonsmokers.[11] Particularly for lung cancer, therefore, the absolute risks from breast cancer radiotherapy could be appreciable for smokers, even if they are small for nonsmokers (because a given proportional increase has less absolute effect on a small risk than on a big risk). Hence, absolute risks of radiotherapy should be estimated separately for smokers and nonsmokers.

The objectives of this study were to estimate the main absolute risks of modern breast cancer radiotherapy. Randomized data on women with long-term follow-up were used to derive rate ratios (RRs) for incident second cancers and causes of death before recurrence of breast cancer and ERRs per Gy for incident primary lung cancer and cardiac mortality. These ERRs per Gy were combined with lung and heart doses from modern regimens and with population-based modern lung cancer and cardiac mortality rates in smokers and in nonsmokers to estimate the absolute risks of modern breast cancer radiotherapy.

METHODS

Systematic Review of Worldwide Modern Lung and Heart Doses

A systematic review of lung and heart doses from recently published (years 2010 to 2015, any language) breast cancer radiotherapy regimens was performed (Data Supplement, Methods S2, Reference S1). Mean organ doses were abstracted (ie, radiation doses averaged across organ volumes). The unweighted average was calculated for all published mean whole-lung doses (averaging ipsilateral and contralateral doses) and mean whole-heart doses. These are termed typical modern doses.

Randomized Trials

Data handling. Data were sought from trials that began before 2000 of radiotherapy versus no radiotherapy or of radiotherapy versus extra surgery (Table 1) in early breast cancer or ductal carcinoma in situ (DCIS). DCIS trials were included because the radiotherapy regimens were similar to those in some breast cancer trials. Trial identification methods are available online.[3,12] For every woman, information was sought about patient and tumor characteristics, allocated treatment, time to first recurrence, time to any contralateral breast cancer or second cancer before recurrence, and date last known to be alive or date and cause of death. Information on molecular subtype, smoking, incident cardiac disease, and lung cancer laterality was unavailable. For lung cancer incidence (after the first decade) and cardiac mortality, the ERRs per Gy were calculated.

Average doses. Radiotherapy details for each trial were extracted from publications and protocols. Regimens were reconstructed on one computed tomography scan with typical anatomy using virtual simulation, three-dimensional computed tomography planning, and sometimes manual planning (Data Supplement, Methods S1).[13] The mean dose to each organ was calculated for the ipsilateral and contralateral lung; the esophagus; the whole heart; and the left-anterior-descending, right, and circumflex coronary arteries. Mean doses were allocated according to trial regimen and breast cancer laterality. The averages of the lung, heart, and esophagus trial doses were weighted by trial size. Contralateral breast and bone marrow doses were not reliably estimable because of exposure uncertainties for structures several centimeters from the beams.

Statistical methods (RRs and ERRs per Gy). RRs of annual events were estimated using standard log rank methods. Analyses were stratified by trial, individual year of follow-up, age at entry, and pathologic nodal status (Data Supplement, Methods S1). Forest plots illustrate proportional risks, and actuarial curves illustrate absolute risks. All confidence intervals are 95%. For lung cancer, the ERR per Gy was calculated by dividing (RR − 1) by the average trial whole-lung dose, because there were too few events to use individual patient doses. Smoking status data were unavailable; therefore, the ERRs were based on all women (smokers and nonsmokers combined). For cardiac mortality, there were sufficient events to investigate the ERR per Gy using trial-specific and laterality-specific doses. These were modeled as a linear function of continuous dose, after assessment for departure from linearity.

Application of Trial ERRs per Gy and Modern Doses to Population Mortality Data

To estimate absolute risks for women today, the ERRs per Gy were multiplied by typical modern lung and heart doses and applied to current smoker and nonsmoker population mortality rates in 5-year age groups (Data Supplement, Methods S1). Background rates of death from lung cancer were taken from nonsmokers in the American Cancer Society Cancer Prevention Study II[14,15] and from smokers in the Million Women Study in the United Kingdom.[11] Background rates of death from ischemic heart disease were taken from those (mostly from 2010) in Western Europe (represented by the original 15 countries of the European Union).[16] These data were also used to estimate the risks for women irradiated at different ages and the effects of smoking cessation.

Table 1. Data Availability From Trials of Radiotherapy Versus No Radiotherapy That Began by the Year 2000

Surgery	No. of Trials	No. of Women	Year Randomly Assigned, (median [IQR])	Woman-Years (thousands) Without Recurrence by Years Since Entry			Deaths	
				< 10	10-19	> 20	Without Recurrence	Any Cause
Mastectomy	36	16,156	1975 (1972-1983)	96	42	13	2,921	11,201
BCS	18	11,655	1992 (1987-1997)	77	18	1	1,270	3,260
Various*	17	9,066	1976 (1972-1983)	59	29	10	1,666	5,512
BCS for DCIS	4	3,904	1992 (1990-1995)	25	5	0	207	372
All trials	75	40,781	1983 (1974-1989)	257	94	24	6,064	20,345

NOTE. Individual trial details are in the Data Supplement Table S3. For balance, unirradiated controls in six 3-arm trials were counted twice, and four of these trials contributed to two categories of surgery. Data sets were not available from 11 trials that included approximately 2,000 women.
Abbreviations: BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; IQR, interquartile range.
*In some of these trials, the control group had more surgery than did the radiotherapy group.

The risk attributable to radiotherapy was taken as the difference in cumulative risks with the ERR per Gy and dose applied and not applied to the population-based rates.

RESULTS

Systematic Review of Worldwide Modern Lung and Heart Doses

A systematic review of all breast cancer radiotherapy dosimetry reports published during 2010 to 2015 identified 214 reports, including 647 regimens with median year of irradiation 2010 (interquartile range [IQR], 2008 to 2011; Data Supplement, Methods S2, Reference S1). The averages of the lung doses were as follows: ipsilateral, 9.0 Gy (IQR, 5.5 to 12.6 Gy), and contralateral, 2.4 Gy (IQR, 0.4 to 3.8 Gy). Averaging the doses to the two lungs, the typical modern whole-lung dose was 5.7 Gy (IQR, 3.4 to 8.3 Gy).[17-19] Average whole-heart doses were as follows: left-sided, 5.2 Gy (IQR, 1.9 to 7.4 Gy), and right-sided, 3.7 Gy (IQR, 1.2 to 5.0 Gy). Averaging these, the typical modern whole-heart dose was 4.4 Gy. Some centers, however, achieved much lower cardiac exposure and reported a whole-heart dose $\leq$ 2 Gy, even in left-sided radiotherapy.[20]

Randomized Trials

Data handling. Information was available from 75 trials involving 40,781 women (Table 1; Data Supplement Table S3), all evenly randomized (1:1 or 1:1:1) with median year of randomization of 1983 (IQR, 1974 to 1989) and median age at randomization of 56 years (IQR, 48 to 64 years). Median follow-up was 10 years (IQR, 5 to 17 years) with 20,345 deaths, 6,064 without breast cancer recurrence. Few women had systemic therapy: 23% (9,470) received tamoxifen and 19% (7,540) received chemotherapy (mainly cyclophosphamide, methotrexate, and fluorouracil).

Average doses. In comparison with typical modern doses, lung and heart doses were higher in the trials: 10 Gy whole lung and 6 Gy whole heart (Data Supplement Table S1: ipsilateral lung, 17.6 Gy; contralateral lung, 1.6 Gy; whole lung, 9.6 Gy; whole heart, 6.3 Gy; left-anterior-descending coronary artery, 13.5 Gy; right coronary artery, 7.7 Gy; circumflex artery, 4.1 Gy; esophagus in trials with internal mammary irradiation, 9.5 Gy, and esophagus in other trials, 0.8 Gy).

RRs and ERRs per Gy. The main risks in the trial were contralateral breast cancer, lung cancer, leukemia, esophageal cancer, and heart disease (Table 2). There was no significant heterogeneity in trial-specific RRs. The RR for contralateral breast cancer was 1.20 (95% CI, 1.08 to 1.33; 881 *v* 673 cancers; $P < .001$; Table 2, Fig 1,

Table 2. Effect of Allocation to RT on Incidence of Second Cancers and on Mortality From Causes Other Than Breast Cancer

Second Cancers and Mortality	No. First Events or Deaths (total woman-years) RT (n = 194,957)	No RT (n = 180,250)	Adjusted Excess* (95% CI)	Rate Ratio (95% CI)	*P*
Second cancer incidence of specified site without prior breast cancer recurrence					
Contralateral breast	881	673	130 (56 to 204)	1.20 (1.08 to 1.33)	< .001
Leukemia	43	23	17 (2 to 33)	1.71 (1.05 to 2.79)	.03
Lung, years 0-9	71	60	5 (−17 to 27)	1.08 (0.76 to 1.53)	.66
Lung, years ≥ 10	94	40	47 (25 to 69)	2.10 (1.48 to 2.98)	< .001
Pleura	3	0	2 (−1 to 5)	—	.18
Esophagus	23	10	13 (3 to 24)	2.42 (1.19 to 4.92)	.01
Pancreas	42	25	14 (0 to 29)	1.64 (0.98 to 2.76)	.06
Stomach	55	63	−12 (−32 to 8)	0.80 (0.55 to 1.17)	.25
Large intestine	164	136	19 (−14 to 51)	1.15 (0.91 to 1.45)	.26
Ovary	68	68	−1 (−22 to 21)	0.99 (0.70 to 1.41)	.95
Endometrium	109	83	20 (−6 to 47)	1.26 (0.94 to 1.69)	.12
Cervix	31	27	2 (−13 to 16)	1.06 (0.62 to 1.83)	.83
Melanoma	32	25	7 (−8 to 21)	1.28 (0.75 to 2.19)	.36
Soft tissue	23	17	6 (−6 to 17)	1.36 (0.71 to 2.59)	.35
Lymphoma	45	41	4 (−14 to 21)	1.09 (0.71 to 1.70)	.69
Other specified site	171	143	5 (−7 to 58)	1.20 (0.95 to 1.51)	.13
All sites except breast	974	761	168 (90 to 246)	1.23 (1.12 to 1.36)	< .001
Death without breast cancer recurrence					
Ischemic heart disease	424	327	90 (39 to 140)	1.31 (1.13 to 1.53)	< .001
Heart failure	63	33	28 (10 to 46)	1.94 (1.27 to 2.98)	.002
Heart valve disease	31	15	14 (1 to 26)	1.97 (1.07 to 3.67)	.03
Other heart disease	187	173	11 (−14 to 36)	1.08 (0.86 to 1.35)	.52
Subtotal: All cardiac	705	548	143 (78 to 208)	1.30 (1.15 to 1.46)	< .001
Cancer of specified site	475	375	67 (12 to 121)	1.19 (1.03 to 1.37)	.02
Other specified cause	638	629	6 (−78 to 91)	1.01 (0.90 to 1.14)	.83
Subtotal: Specified cause	1,818	1,552	216 (111 to 322)	1.16 (1.08 to 1.25)	< .001
Unspecified cause	1,413	1,281	153 (58 to 247)	1.14 (1.05 to 1.24)	.002
All causes of death except breast cancer	3,231	2,833	369 (228 to 510)	1.15 (1.09 to 1.22)	< .001

NOTE. Cancer incidence excludes nonmelanoma skin cancer. Other specified sites include uterus, part unspecified.
Abbreviation: RT, radiotherapy.
*The adjusted excess number of events (or deaths) in the RT group is calculated as twice the log rank observed minus expected (Data Supplement, Methods S1) and allows for RT delaying recurrence.

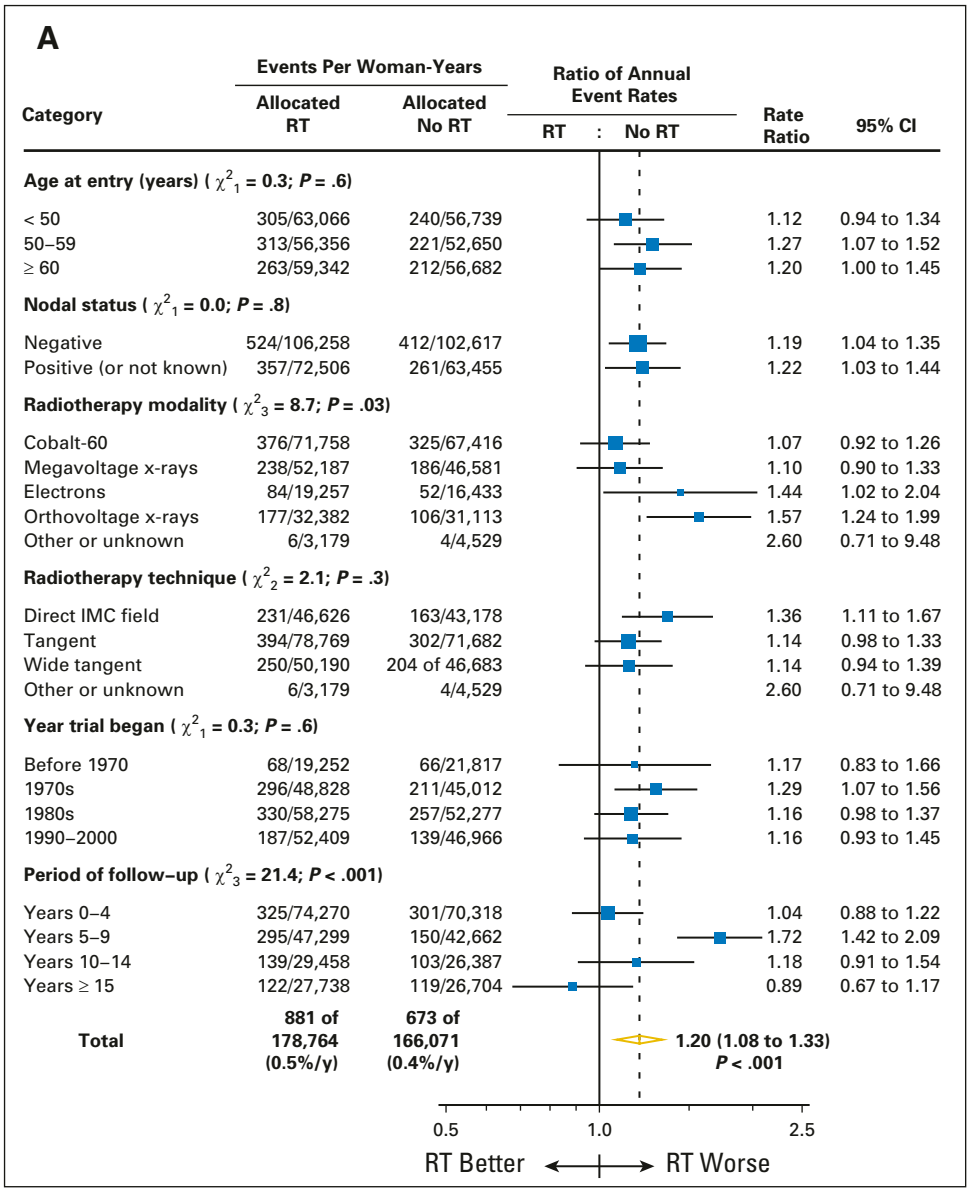

Fig 1. Effect of allocation to radiotherapy (RT) on (A) contralateral breast cancer and on (B) lung cancer incidence (≥ 10 years). IMC, internal mammary chain.

Data Supplement Figure S4). Contralateral cancers were not mainly misclassified recurrences, because incidence was unrelated to nodal status (Data Supplement Table S5). The contralateral breast cancer RR was greater in the old trials of orthovoltage (low-energy) radiotherapy (RR, 1.57; 95% CI, 1.24 to 1.99) than in the other trials (RR, 1.12; 95% CI, 1.00 to 1.26; Data Supplement Figs S4, S5). But in both cases, contralateral breast radiation doses were not reliably known, so the contralateral breast cancer ERR per Gy could not be estimated. In the non-orthovoltage trials, the absolute 15-year increase in contralateral breast cancer risk was 1.0% (95% CI, 0.2 to 1.8; 7% *v* 6%; Data Supplement Fig S5).

Allocation to radiotherapy increased the incidence of primary lung cancer (Table 2, Data Supplement Figs S7, S9). These cancers were not mainly misclassified pulmonary metastases, because their incidence was unrelated to nodal status (Data Supplement Table S7). There was no significant excess in the first decade after radiotherapy. Thereafter, there were 94 versus 40 cases (RR, 2.10; 95% CI, 1.48 to 2.98; $P < .001$; Fig 1), corresponding to 0.11 (95% CI, 0.05 to 0.20) ERR per Gy.

The incidence RR, radiotherapy versus control, for second cancers other than breast or lung was 1.19 (95% CI, 1.07 to 1.32; Data Supplement Fig S10). The main components were leukemia (RR, 1.71; 95% CI, 1.05 to 2.79) and esophageal cancer (RR, 2.42; 95% CI, 1.19 to 4.92, with 30 of the 33 cases occurring in the trials in which radiotherapy involved the internal mammary chain and supraclavicular fossa; Table 2). ERRs per Gy were not calculated for leukemia or esophageal cancer because both CIs were wide and bone marrow doses were not estimable.

All-cause mortality among women without breast cancer recurrence was increased by radiotherapy (RR, 1.15; 95% CI, 1.09 to 1.22; Table 2; Data Supplement Figs S1-S3, Table S4), predominantly because of cardiac disease (RR, 1.30; 95% CI, 1.15 to 1.46). Most of the excess cardiac mortality was from ischemic heart disease (RR, 1.31; 95% CI, 1.13 to 1.53; Table 2). However, the main analyses are of all

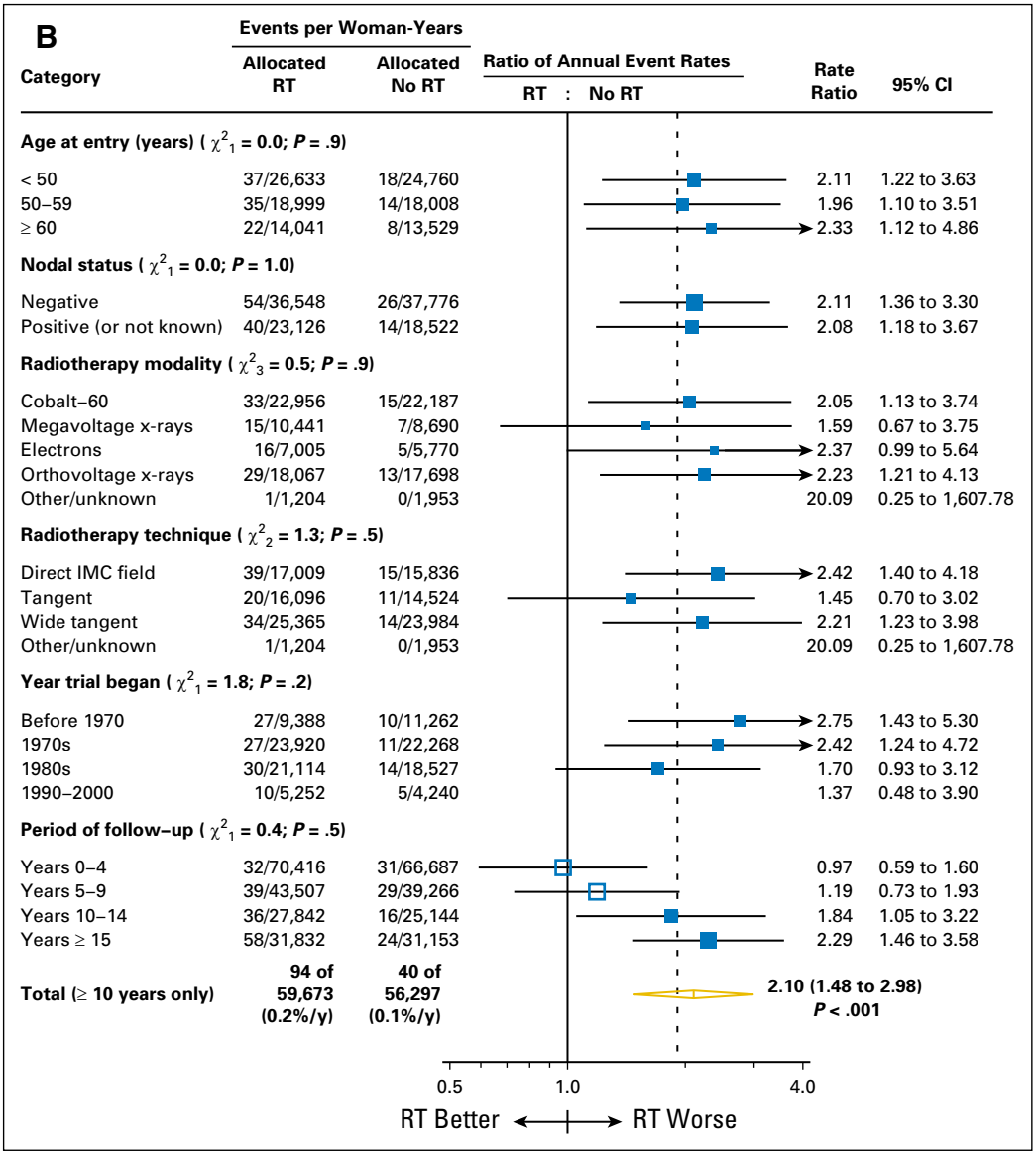

Fig 1. (Continued).

cardiac mortality, defined as mortality from all circulatory disease with the exception of stroke or pulmonary embolism (Data Supplement Fig S14). Some excess cardiac mortality emerged within 5 years, with the RR in years 0 to 4 similar to that in years ≥ 15. However, because cardiac mortality increases steeply with age, the absolute excess risk was much greater in the later time period (Data Supplement Figs S11-S12). The cardiac mortality RR, radiotherapy versus no radiotherapy, was strongly related to the estimated whole-heart radiation dose. Analyses that related risk to the trial radiotherapy regimen and to breast cancer laterality yielded an ERR per Gy of 0.041 (95% CI, 0.024 to 0.062; $P < .001$; Fig 2).

Application of Trial ERRs per Gy and Modern Doses to Population Mortality Data

The typical whole-lung dose from modern regimens was approximately 5 Gy. Combining this with the 0.11 ERR per Gy for lung cancer > 10 years after radiotherapy and with the population-based lung cancer rates[11,14,15] yielded estimates of lung cancer risks by age 80 years from typical modern breast cancer regimens (Fig 3A; Data Supplement Fig S15, Table S9). For a 50-year-old nonsmoker, a 5-Gy whole-lung dose that increases lung cancer rates by approximately 55% would increase lung cancer mortality before age 80 years from approximately 0.5% to 0.8% (ie, an estimated absolute increase of 0.3%). In contrast, for a 50-year-old woman who has smoked since adolescence and does not stop, a 55% increase in the lung cancer mortality rate would change her risk of death from lung cancer before age 80 years from approximately 9.4% to 13.8% (an absolute increase of 4.4%). Smoking cessation at the time of radiotherapy would reduce this estimate of the radiation-related increase in lung cancer mortality from 4.4% to 1.3% (Data Supplement Table S9).

Lung doses published during 2010 and 2015 varied according to regimen (IQR, 3.4 to 8.3 Gy). If a woman's whole-lung dose was

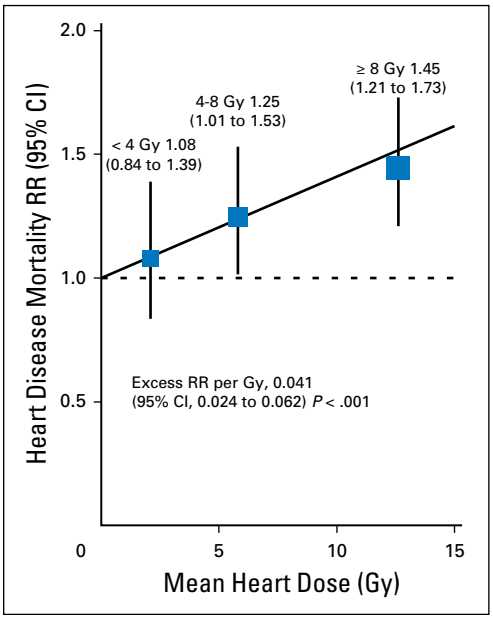

Fig 2. Heart disease mortality rate ratio (RR) by trial-specific mean radiation dose to the heart. The line was estimated using doses for individual women. Squares (with areas proportional to information content) show dose categories < 4, 4 to 8, and > 8 Gy, with mean doses of 2.1, 5.8, and 12.6 Gy.

only one half the typical dose, these absolute excess risks would be halved, but if it exceeded the typical dose of approximately 5 Gy, the estimated risks would be correspondingly higher.

The typical whole-heart dose from modern radiotherapy regimens was approximately 4 Gy. Combining 4 Gy with the 0.041 ERR per Gy for cardiac mortality, cardiac mortality risks from modern breast cancer radiotherapy were estimated. On the basis of 2010 female death rates in the 15 European Union member states in Western Europe,[16] the estimated risk of death before age 80 years as a result of heart disease was 1.8% for a nonsmoker and 8.0% for a smoker.[11] If, as this study suggests, a 4-Gy mean heart dose multiplies these risks by approximately 1.16, then the absolute increase in cardiac mortality would be 0.3% for a nonsmoker and 1.2% for a smoker (Fig 3B). Whole-heart doses in modern regimens varied widely (IQR for left radiotherapy, 1.9 to 7.4 Gy; IQR for right radiotherapy, 1.2 to 5.0 Gy). For doses > 4 Gy, the absolute hazards would be somewhat greater. For cancer centers reporting whole-heart doses of < 2 Gy, the estimated excess cardiac mortality would be less than half as great.

DISCUSSION

Breast cancer radiotherapy has changed since these trials, with a reduction in lung and heart radiation doses. However, the ERRs per Gy in the past trials remain relevant and can be used to estimate risks from modern radiotherapy.

For lung cancer, radiotherapy had its main effect > 10 years later (Fig 1, Data Supplement Figs S6-S7). The lack of any material early hazard and the substantial hazard during the second decade in these randomized trials are confirmed by nonrandomized SEER registry data (Data Supplement Table S8).[10] The ERR per Gy in this study is quantitatively consistent with estimates from published epidemiologic studies, which together included 334 lung cancers in patients with known smoking status (Data Supplement Fig S8). Lung cancer is rare in nonsmokers; only 52 of the 334 cancers in those epidemiologic studies were in nonsmokers. Although smoking information was unavailable for women in the trials, our estimate of the ERR per Gy, as in the epidemiologic studies, will be based primarily on the findings among smokers; hence it is likely to be reliable for them. For nonsmokers, even if the ERR per Gy is not exactly the same as in smokers, their absolute risk would still be small.

Because quitting smoking greatly reduces lung cancer incidence,[11,15] the estimated absolute increase in lung cancer mortality from radiotherapy in ex-smokers is likely to be much closer to that in never-smokers than in current smokers (Data Supplement Table S9). Even smoking cessation at the time of radiotherapy should substantially reduce the risk of radiation-induced lung cancer,[11,15] because cessation greatly reduces the

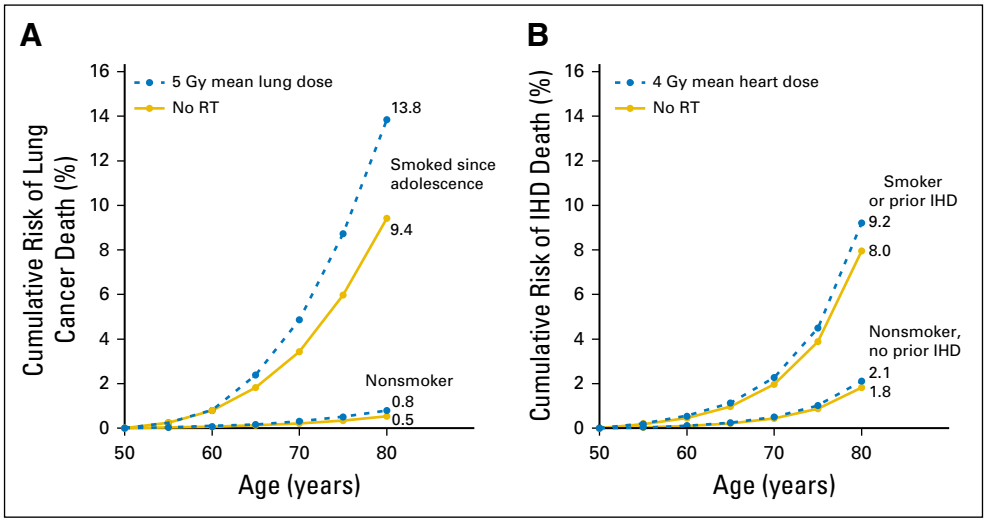

Fig 3. Estimated effects among 50-year-old smokers and nonsmokers of typical modern radiotherapy (RT) regimens on mortality from (A) lung cancer and (B) ischemic heart disease (IHD). Epidemiologic estimates of the risks without radiotherapy are multiplied by the rate ratios attributed to 5 Gy whole-lung dose and 4 Gy whole-heart dose (Data Supplement Methods S1).

risk > 10 years later, which is when the main effects of radiotherapy on lung cancer occur (Data Supplement Table S9). Therefore, by quitting smoking at the time of radiotherapy, smokers would reduce their absolute risk of radiation-induced lung cancer and would achieve a much greater absolute reduction in other tobacco-attributable risks.[11] For smokers irradiated after age 70 years, radiotherapy would be expected to have no material effect on lung cancer risk before age 80 years.

Radiotherapy increased contralateral breast cancer as in nonrandomized studies (Data Supplement Table S6).[21-23] In the trials, the risk was greatest for women who received orthovoltage radiotherapy (Fig 1), which tends to deliver scattered radiation to nearby organs[24] but is rarely used nowadays. Considering just the women in non-orthovoltage trials, the absolute radiation-induced risk of contralateral breast cancer was only approximately 1%, and many of these cancers could be treated successfully. Since these trials, contralateral breast doses have decreased[24-27]; moreover, contralateral breast cancer incidence is reduced by effective systemic therapy.[5,6,28] Hence, the absolute risk of contralateral breast cancer from modern radiotherapy should be well under 1%, and the risk of death from this late effect should be smaller still.

Radiotherapy increased esophageal cancer incidence as in some nonrandomized studies.[29-31] Most cases arose in trials in which the regional lymph nodes were irradiated with fields that included part of the esophagus. It is now usual to angle fields away from the esophagus, so the absolute esophageal cancer risk from modern breast cancer regimens should be very small.[32,33]

For cardiac death, the estimated absolute cardiac hazards are much smaller now than in these trials, because population cardiac mortality rates are now much lower than they were 30 years ago. Moreover, the absolute cardiac risks from radiotherapy will continue to decrease if population heart disease death rates continue to decrease.

Risks were estimated for typical modern radiotherapy in typical populations of women. But heart and lung doses in breast cancer regimens vary, as do population disease rates; therefore the absolute risks and the effect of smoking cessation will vary for individual women. The absolute benefits of radiotherapy also vary with cancer characteristics. For women with invasive cancer, radiotherapy reduces breast cancer mortality by a few percentage points. For women with DCIS, the benefit is smaller. The absolute risks from radiotherapy for some smokers who continue smoking could exceed the absolute benefit. For example for a 50-year-old long-term smoker with a small, node-negative breast cancer, her estimated absolute benefit from radiotherapy after breast-conserving surgery is an approximately 2% to 5% reduction in breast cancer mortality,[2] whereas her estimated absolute risks from typical modern radiotherapy are approximately 4% for lung cancer and approximately 1% for cardiac mortality if she does not quit smoking. These findings reinforce the need to limit lung and heart doses without unduly compromising the dose to the target tissues, and the need for smokers to stop smoking.

This study has the advantage of being randomized; therefore, any definite excesses reflect causality. However, it has some limitations. Causes of death were not all known, and data on smoking habits were unavailable. Lung and heart doses were estimated retrospectively, and (with the exception of laterality) only trial-level rather than individual-level radiotherapy information was used. Hence, the estimates of ERRs per Gy cardiac mortality and lung cancer depend on trial-level doses (not individual patient doses) being approximately correct. Lung doses from the trial regimens have not been reported elsewhere, but the estimated cardiac doses from trial regimens are similar to other published estimates.[13,34-36] Our analyses rely on the assumption that the risks per Gy lung and heart dose have not changed over time (ie, that if the doses have halved, the risks have halved). However, the biologic effects of radiotherapy are unlikely to have changed over time, and the risks per Gy lung or heart dose in this study are consistent with other published estimates for patients irradiated in different decades[37] (Data Supplement Fig S8). The proportional increase in cardiac mortality of 0.041 per Gy is somewhat lower than a recent population-based estimate of a 0.074 per Gy increase in major coronary events,[37] but the difference is not statistically significant and the end points differ.

Information on incident heart disease was unavailable; therefore, it was not possible to study the relationship between heart dose and incident heart disease. Any history of heart disease prior to radiotherapy was also unknown, and it could have substantially increased the absolute cardiac effects of radiotherapy. Few women in these trials received anthracyclines, and none received trastuzumab, so the combined cardiac effects of these cardiotoxic systemic therapies with radiotherapy could not be assessed. However, although these systemic therapies can affect the absolute risks of heart disease, they may not materially affect the ERR per Gy.

For long-term smokers irradiated today, the estimated combined risks from radiotherapy are a few percentage points if smoking continues, which may outweigh the reduction in breast cancer mortality; however, smoking cessation substantially reduces risk. For healthy nonsmokers, the estimated absolute risks of lung cancer or cardiac mortality from radiotherapy add up to < 1%, which, for most women, is much smaller than the benefit from radiotherapy.[1-5]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Carolyn Taylor, Richard Peto, Paul McGale
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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials

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