Supplementary Material

Estimating the risks of breast cancer radiotherapy: Evidence from modern radiation doses to the lungs and heart and from previous randomised trials

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Writing committee for the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

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Methods S1. Details of statistical and dosimetry methods

(a) Statistical methods

Coding of cause of death and second cancer incidence

For each woman who had died, trialists supplied us with the International Classification of Diseases (ICD) for underlying cause of death or a text description of the underlying cause of death. These were reviewed by an oncology consultant and coded into categories of disease types (see Table S2). Likewise trialists supplied ICD or text descriptions of any incident malignancies occurring after randomisation.

Cancer deaths from unknown primaries were included with breast cancer deaths. When no recurrence was reported before breast cancer death, distant recurrence was assumed to have just preceded it. Deaths from an unknown cause without recorded recurrence were taken as non-breast-cancer deaths, as most occurred many years after trial entry, when non-breast-cancer mortality predominated.

If a trial did not supply cause-specific mortality then it was dropped from analyses of cause-specific mortality. If a trial did not follow-up for malignant events it was dropped from incident cancer analyses. Thus the total woman-years vary from analysis to analysis.

Women assigned to radiotherapy have slightly longer recurrence-free survival and therefore are at risk of death without recurrence (or second cancer) for slightly longer. To prevent delayed recurrences causing bias, the log-rank analysis (see below) covered only the period before recurrence i.e., data were censored at the first recurrence.

Methodology for logrank analyses

Let 0 denote the observed number of events in the radiotherapy allocated group, and let E denote the number that would have been expected at the period specific events rates in the radiotherapy and no radiotherapy groups combined, and let V denote the variance of the logrank statistic (O-E). A positive value for (O-E) then suggests hazard, with the number of deaths caused by radiotherapy being approximately 2*(O-E). The ratio (O-E)/V is the "one-step" estimate of the natural log of the event rate ratios (RR, radiotherapy versus no radiotherapy). Hence, the one-step estimate of RR is exp((O-E)/V) with 95% confidence limits RR/k, RR*k, where k=exp(1.96/$\sqrt{V}$).

Statistical analyses were stratified. Logrank statistics were calculated for each combination of trial, individual follow-up year, age at entry (<40, 40-49, 50-59, 60-69, 70+) and pathological nodal status (0, 1-3, or 4+ positive nodes, clinical negative, or clinical positive/unknown) and then summed. In multiarm trials, for balance, control groups were counted twice.

For the main endpoints, forest plots show proportional risk reductions. Detailed subgroup analyses explore whether the reductions depend on patient or tumour characteristics. Acturial curves illustrate absolute risks in various subgroups.

Statistically reliable subgroup analyses require the overall χ^2 1 for the RR (radiotherapy vs control) in all subgroups to be large (eg, at least 25, but preferably 50, or even 100). The overall χ^2 1 gets partitioned between the subgroups in approximate proportion to numbers of events. So if the χ^2 1 in a subgroup was only about 10, chance could well make it non-significant or null.

Logrank analyses were performed using Stata Statistical Software, release 13.1 (StataCorp) and R release 2.13.2.

Tests for trend and heterogeneity

Where the effect of radiotherapy was evaluated in subgroups (e.g. in three age groups), then the following procedures were used to test for a trend where there was a natural ordering (e.g. from younger to older), or for heterogeneity where no natural ordering exists.

Test for trend

The subgroups were numbered in their natural order (e.g. 1 = age <50, 2 = age 50-59, 3 = age 60+). O-E and its variance, V, were calculated separately for the treatment effect in each subgroup (e.g. O_1-E_1 and V_1 for subgroup 1). Let k denote the number of subgroups with non-zero variance. Next, the following values were calculated:

$A = V_1+V_2+V_3$

$B = 1.V_1+2.V_2+3.V_3$

$C = 1.1.V_1+2.2.V_2+3.3.V_3$

$D = (O_1-E_1)+(O_2-E_2)+(O_3-E_3)$

$E = 1.(O_1-E_1)+2.(O_2-E_2)+3.(O_3-E_3)$

$F = (O_1-E_1)^2/V_1+(O_2-E_2)^2/V_2+(O_3-E_3)^2/V_3$

A test for a trend between the rate ratios produced by treatment in these different subgroups may be based on calculation of the quantity (E-DB/A). If there is no real heterogeneity between the rate ratios, then it can be shown that this quantity will differ only randomly from zero, and that its standard error (SE) will be approximately √(C-BB/A). Values more extreme than ±1.96 SE would therefore correspond approximately to P<0.05. Provided the effect is not large, the statistical properties of O-E and V imply that this trend test is asymptotically efficient at detecting a steady multiplicative trend in the rate ratios.

Test for heterogeneity

A test for heterogeneity was obtained by calculating the quantity (F-DD/A). If there is no real heterogeneity between the rate ratios in the k different subgroups being considered, then this quantity will be distributed approximately as a standard chi-squared distribution with k-1 degrees of freedom.

Test for "interaction" between the effects of radiotherapy in just two different subgroups

In this case, the tests for trend and for heterogeneity (with k=2) yield identical significance levels.

Radiotherapy modality and technique

For proportional risks of various radiotherapy modalities, women were grouped according to whether their radiotherapy involved cobalt-60, megavoltage X-rays, electrons or orthovoltage X-rays. For the few trials where women were treated with more than one modality, that with the highest radiation scatter dose was assigned if it was not possible to tell which modality was given to a particular woman. This may have the effect of biasing towards the null.

Methodology for estimating the cardiac dose-response relationship

Each woman in each trial was assigned a dose based on the radiotherapy technique used in the trial and on the laterality of her breast cancer. If laterality information was not available for a particular woman then she was assigned the average of the doses for irradiation of right-sided and left-sided breast cancer in the trial she was randomised into.

Stratification was as for logrank analyses. It was assumed there was zero risk at zero dose. The rate of heart disease mortality was modelled as $b_s(1+\beta_1*d)$, where b_s was the stratum-specific rate of heart disease mortality in the absence of radiotherapy, d was the dose (or EQD2) of cardiac radiation (in Gy), and β_1 was the percentage increase in the rate of heart disease mortality per gray. The form $1+\beta_1*d$ was chosen for the dose–response relationship

because a wide variety of functions are approximately linear for small values of d. The adequacy of $1+\beta_1$*d for summarizing the dose–response relationship was examined by carrying out analyses based on categories of radiation dose.

Further models including terms for dose squared ($+\beta_2$*d*d) and a decline in risk at high doses (*exp($-\beta_2$*d)) were used to investigate any departure from linearity. Sensitivity analyses excluded the effect of the few trials with inadequate information on dosage, and excluded patients with breast cancer that was bilateral or of unknown laterality. Mean doses to the three separate coronary arteries were assessed to check for any improvement of risk estimation (Figures S15-S16). No significant departure from linearity was found and the addition of coronary artery doses to the risk model did not improve estimation.

Significance tests were two-sided, and both significance tests and confidence intervals were based on the likelihood ratio. Calculations were performed with the use of EpiWin, release 1.8 (Hirosoft International).

Methodology for calculating estimated risks of death from lung cancer and ischaemic heart disease

Results in figure 3 show the effects of radiotherapy on estimated risks of death from lung cancer and ischaemic heart disease for a woman irradiated at age 50 years. These were estimated by applying the proportional excess per Gy for lung cancer (figure 1 and main text), to representative population-based lung cancer death rates in smokers and non-smokers. The derived dose-response relationship for heart disease death (figure 3) was similarly applied to representative populations.

Lung cancer

Background rates of death from lung cancer for non-smokers and smokers were assumed to be equal to those of non-smokers in the American Cancer Society Cancer Prevention Study II [Thun 2013] and smokers in the UK Million Women Study [Pirie 2013] respectively. Estimated risks were calculated for a typical woman who was 50 years old at the time of her breast-cancer diagnosis who received either no radiotherapy or radiotherapy with a mean lung dose of 5 Gy. The excess rate ratio for lung cancer from radiotherapy, 0.11 per Gy, was assumed to start at age 60.

Ischaemic heart disease

Background rates of death from ischaemic heart disease (IHD) were assumed to be equal to those (mostly 2010) in Western Europe (represented by the original 15 countries of the European Union, EU-15). For non-smokers IHD rates were taken to be 2/3rds that of the EU-15 population and for smokers 3 times. Risk of IHD death in women with IHD prior to radiotherapy was assumed to be similar to that of a smoker. Estimated risks were calculated for a typical woman who was 50 years old at the time of her breast-cancer diagnosis who received either no radiotherapy or radiotherapy with a mean heart dose of 4 Gy. The excess rate ratio for heart disease from radiotherapy, 0.041 per Gy, was assumed to start at age 50.

References

Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. N Engl J Med 2013; 368: 351-64.

Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. Lancet 2013; 381: 133-41.

(b) Radiation dosimetry methods (methods and the main regimens are summarised in Taylor 2007)

Information on regimens

Radiotherapy details of regimens used in each of the 75 trials were sought from a variety of sources including trial publications, protocols and correspondence with trialists. Further general details of breast cancer radiotherapy planning and delivery worldwide during past decades were obtained to enable authentic replication [Taylor 2007]. The items available on the radiotherapy given in each trial were documented. The following four items were judged to be needed for accurate reconstruction of each regimen: (1) Targets or regions irradiated (2) Radiation dose delivered to each region (3) Radiotherapy technique used and (4) Beam energies applied. Further items e.g. patient treatment position were judged to be useful, but not essential for reconstruction. Trials were categorised according to the information available.

For 48/75 trials, information was available on all of items 1-4. The other 27/75 trials did not specify one or more of these four items. Organ doses estimated for these trials will have inherently higher uncertainties. Analyses just of the 48 trials with adequate information on regimens yielded similar estimates of the excess RR per Gy heart dose to analyses that included all 75 trials.

Contouring of cardiac structures, lungs and oesophagus

The heart and coronary arteries were contoured by a radiation oncologist and reviewed by a radiologist. The cranial limit of the heart included the right atrium and excluded the pulmonary trunk, ascending aorta and superior vena cava. The lowest contour of the heart was the caudal myocardial border. The scans were not contrast-enhanced. Therefore, on some images, the coronary arteries were not visible and their location was inferred using visible, reliable landmarks: the anterior interventricular, left atrioventricular and right atrioventricular grooves. Due to the short length of the left main coronary artery, its contour was included with that of the left anterior descending (LAD) coronary artery.

The ipsilateral and contralateral lungs were contoured using an automatic contouring tool, and modified manually where appropriate. The oesophagus was visible, and contoured manually on each CT slice.

Regimen reconstruction

A technique based upon virtual simulation and computed tomography (CT) 3-dimensional treatment planning was used to reconstruct radiotherapy regimens. Dose distributions were calculated using treatment planning systems Helax TMS version 6.1B, Nucletron Ltd, Veenendaal, the Netherlands and Varian Eclipse^{TM} version 10.0.39. Field borders, beam arrangements and machine parameters for each radiotherapy regimen were defined using virtual simulation with emphasis on the surface reconstruction function.

The treatment parameters and patient and organ at risk outlines were exported to the computerised treatment planning system and dose distributions were calculated. Dose calculation algorithms were: the collapsed cone superposition convolution algorithm and the analytical anisotropic algorithm for photon plans, Monte Carlo for electron plans and pencil beam for cobalt plans.

For each regimen, dose-volume histograms (DVHs) were generated for the heart and for the LAD and right and circumflex coronary arteries and for the ipsilateral lung, contralateral lung and oesophagus. From these, estimates of mean and maximum dose and percentage volume irradiated to different doses were obtained.

Dose distributions for several 250 kV regimens and iridium wire implants were also derived. This involved generating scaled hard-copies of appropriate CT slices on which isodose distributions for kilovoltage or iridium wire implants were superimposed. Manual planning techniques incorporating lung correction were employed to generate dose distributions. The physical density of lung was taken to be 0.25 g/cm^{-3}. The proportion of each structure included

within each isodose line was calculated manually and used to plot DVHs. These were typically based on three CT slices per radiotherapy plan.

Heart and coronary artery doses were calculated for women in 45 trials with heart disease deaths. Lung doses were calculated for women in 29 with lung cancers in the second decade after radiotherapy. Oesophagus doses were calculated for women in 19 trials with oesophageal cancers.

Validation of the 'representative patient'

Each regimen was reconstructed on a 'representative patient'. To ensure that the doses based on this patient were representative of those received by patients with a range of different anatomies, four commonly used regimens: left and right tangential pair irradiation and left and right direct IMC irradiation were reconstructed on the 'representative patient' and on four other patients taken at random from the CT planning database, for comparison. These four regimens were chosen since they represented the most commonly used types of breast cancer irradiation in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) trials.

Heart dose for the 'representative patient' was near the middle of the dose range of the 5 random patients for left- and right-sided tangential pair and direct IMC irradiation, thus validating the use of her CT scans for the reconstruction of radiotherapy regimens used in the trials. A further study of inter-patient variability in heart dose using four similar regimens reconstructed on 20 patients is reported in Taylor 2007.

Trials in which women received different regimens

In a few trials, the radiotherapy regimens received by an individual woman depended on nodal status or the position of the tumour in the breast. In some other trials, regimens varied according to the availability of certain beam modalities and energies in different radiotherapy centres. For some of these trials, the proportions of women who received each regimen were recorded, or could be estimated. For example in the Danish Breast Cancer Cooperative Group (DBCG) 82 b and c trials, 8% of irradiated women were recorded as receiving orthovoltage irradiation, and the rest received megavoltage irradiation [Nielsen 2005]. These proportions were used to calculate average organ doses for women who received left- and right-sided radiotherapy in each trial. In other trials these proportions were not recorded and equal proportions of women were assumed to have received each radiotherapy regimen. For example, in the South Sweden breast cancer trial [Tennvall-Nittby 1993] the direct internal mammary field was delivered using either electron, cobalt-60 or 6 MV irradiation. The proportions of women receiving each beam type were not available. It was therefore assumed that a third of irradiated women received electron internal mammary irradiation, a third received cobalt-60, and the remaining third received 6 MV irradiation.

Calculation of equivalent dose in 2 Gy fractions (EQD2) in the EBCTCG trials

EQD2 doses were calculated using the linear-quadratic model from dose volume histograms (DVH) using an alpha-beta ratio of 2 Gy [Schultz-Hector 2007].

$$EQD2 = nd \frac{(d + \alpha/\beta)}{(2 + \alpha/\beta)}$$

n = number of fractions
d = dose per fraction
α/β = alpha-beta ratio

For orthovoltage radiotherapy, a correction factor of 1.1 was used to account for the enhanced biological effectiveness of low energy irradiation [Fuller 1992].

References

Fuller SA, Haybittle JL, Smith REA, et al. Cardiac doses in post-operative breast irradiation. Radioth Oncol 1992;25:19-24.

Host H, Brennhovd IO, Loed M. Postoperative radiotherapy in breast cancer – long-term results from the Oslo study. Int J Radiat Oncol Biol Phys 1986;12:727-732.

Nielsen HM, Overgaard J, Grau C et al. Audit of the radiotherapy in the DBCG 82 b&c trials – A validation study of the 1538 patients randomised to postmastectomy radiotherapy. Radioth Oncol 2005;76:285-292.

Schultz-Hector S, Trott K-R. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? Int J Radiat Oncol Biol Phys 2007;67:10-18.

Taylor CW, Nisbet A, McGale P, Darby SC. Cardiac exposures in breast cancer radiotherapy: 1950s-1990s. Int J Radiat Oncol Biol Phys 2007; **69:** 1484-95.

Tennvall-Nittby L, Tengrup I, Landberg T. The total incidence of loco-regional recurrence in a randomised trial of breast cancer TNM stage II. Acta Oncologica 1993;32:641-646.

Table S1. Estimated average mean doses to organs at risk for women in Early Breast Cancer Trialists' Collaborative Group (EBCTCG) trials.

1a) Average doses to heart, coronary arteries, lung, and oesophagus

Organ at risk*	Number of trials	Number of women	Average dose (Gy)	IQR (Gy)
Heart	45	29,664	6.3	2.2-8.5
LAD coronary artery	45	29,664	13.5	1.4-21.9
Right coronary artery	45	29,664	7.7	2.2-11.8
Circumflex coronary artery	45	29,664	4.1	1.0-4.1
Both lungs combined	29	5248	9.6	3.4-11.1
Ipsilateral lung	29	5248	17.6	6.6-20.7
Contralateral lung	29	5248	1.6	0.3-2.0
Oesophagus	19	8279	8.4	1.2-10.7
Oesophagus (IMC trials)	16	7272	9.5	3.5-10.5
Oesophagus (non-IMC trials)	3	1007	0.8	0.5-1.0

*Heart and coronary artery doses were calculated for women in 45 trials with heart disease deaths. Lung doses were calculated for women in 29 trials with lung cancers in the second decade after radiotherapy. Oesophagus doses were calculated for women in 19 trials with oesophageal cancers.

1b) Average doses to the heart by decade trial started and breast cancer laterality in 45 EBCTCG trials with heart disease deaths

Decade trial started	Average mean heart dose (Gy)		
	Right-sided	Left-sided	Unknown laterality
1950s			9.6
1960s	7.7	13.7	5.7
1970s	4.9	11.7	9.4
1980s	1.8	5.3	3.7
1990s	1.5	4.9	3.1

1c) Average doses to lung by decade trial started in 29 EBCTCG trials with lung cancer events in the second decade after radiotherapy

Decade trial started	Average mean lung dose (Gy)		
	Both lungs	Ipsilateral lung	Contralateral lung
1950s	12.0	23.0	1.0
1960s	9.5	17.3	1.6
1970s	9.3	16.8	1.7
1980s	10.2	18.8	1.6
1990s	3.2	6.0	0.2

Table S1 contd. Estimated average mean doses to organs at risk for women in Early Breast Cancer Trialists' Collaborative Group (EBCTCG) trials.

1d) Average doses to oesophagus by decade trial started in 19 EBCTCG trials with oesophagus cancer events

Decade trial started	Average mean oesophageal dose (Gy)	
	Mean dose	IQR
1960s	9.7	1.8-13.4
1970s	5.6	3.9-7.2
1980s	12.3	0.8-21.1
1990s	0.4	0.4-0.4

1e) Correlations between estimated average doses to cardiac organs at risk in the trials in the present study.

i) Correlation between average doses

	Heart	LAD	Right CA	Circumflex
Heart	1.00			
LAD	0.76	1.00		
Right CA	0.49	-0.02	1.00	
Circumflex	0.89	0.80	0.23	1.00

ii) Correlation between average mean doses and average mean EQD2 doses

		Mean dose			
		Heart	**LAD**	**Right CA**	**Circumflex**
Mean EQD2	**Heart**	0.99			
	LAD		0.98		
	Right CA			0.99	
	Circumflex				0.96

Abbreviations: LAD=Left anterior descending, CA=coronary artery, EQD2=Equivalent dose in 2 gray fractions (calculated using an α/β of 2 Gy [Schultz-Hector 2007])

Reference

Schultz-Hector S, Trott KR. Radiation-induced cardiovascular diseases: is the epidemiologic evidence compatible with the radiobiologic data? *Int J Radiat Oncol Biol Phys* 2007; **67:** 10-18.

Table S2. Groupings of disease categories by International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)

Disease category	ICD-10
Infectious/parasitic (excluding viral hepatitis)	A00-A99, B00-B99. Excluding: B15-B19
Hepatic disease	B15-B19, K70-K77
Oesophageal cancer	C15
Gastric cancer	C16
Colorectal cancer	C18-C21
Primary liver cancer	C22. Excluding: C22.9
Liver cancer, unspecified*	C22.9, D37.6
Bile duct / gallbladder cancer	C23, C24
Pancreatic cancer	C25
Lung cancer	C33-C34
Bone cancer	C40, C41
Melanoma	C43
Pleura	C45.0
Soft tissue cancer	C48, C49
Breast cancer or its metastases	C50
Cervical cancer	C53
Endometrial cancer	C54
Uterine cancer, part unspecified	C55
Ovarian cancer	C56-C57
Renal cancer	C64
Bladder cancer	C67
Brain / CNS cancer	C70-C72
Thyroid cancer	C73
Secondary (ie metastatic disease), primary unspecified*	C76-C80. Excluding: C80.9
Unknown second primary, non-breast	C80.9
Lymphoma	C85, C90
Leukaemia	C88, C91, C92
Other second primary of specified site (apart from breast cancer and non-melanoma skin cancer)	C00-C75, C81-C84, C86-C89, C93-C97. Excluding: C15-C16 , C18-C25, C33-C34, C40-C41, C43, C45.0, C48, C49, C50, C54, C55, C56-C57, C53, C64, C67, C70-C73
Valve disease (including cases with mention of ischaemic heart disease or heart failure)	I05-I09, I33-I39
Ischaemic heart disease	I20-I25
Heart failure (without mention of ischaemic heart disease or myocardial infarction)	I50
Arrhythmia	I44-I49
Deep vein thrombosis and pulmonary embolism	I26 , I80, I82, O88.2
Cerebrovascular	I60-I69
Other circulatory (including 'Acute cardiac' and 'Chronic cardiac')	I00-I99, R00-R02, R57, R96. Excluding: I05-I09, I20-I26, I33-I39, I44-I49, I50, I60-I69, I80, I82
Non-pneumonia respiratory	J00-J99, R04-R09. Excluding: J12-J18 , J41-J44
Pneumonia	J12-J18
Chronic obstructive pulmonary disease	J41-J44
External cause	S00-Y98
Other specified disease	All other ICD codes

* These are grouped with breast cancer or its metastases.

Table S3. Trials included, regions irradiated, median age at entry, distribution of woman-years since entry and, in each trial arm (RT or No RT), numbers of deaths without breast cancer recurrence and woman-years. AF=axilla and/or supraclavicular fossa, B=breast, BCS=breast conserving surgery, CW=chest wall, IMC=internal mammary chain, RT=radiotherapy, S= boost to scar. Parentheses indicate only some women received radiotherapy to this region. * For balance, control patients in 3-way trials or trial strata count twice in totals of deaths/women. † Same polychemotherapy and/or tamoxifen in each trial arm.

Trial reference, type, year started, and name			Regions irradiated	Median age	Woman-years since entry			Deaths without recurrence /woman-years	
					<10	10-19	20+	RT	No RT
Breast conservation, generally with axillary dissection: RT vs not									
1	1976	NSABP B-06	†B	51	8025	4649	1064	115/7965	67/5773
2	1981	Uppsala-Örebro	B	62	2865	1332	19	48/2220	51/1996
3	1982	St George's London	†B+AF	51	2786	1099	79	15/2194	8/1770
4	1984	Ontario COG	B+S	56	5633	667	0	33/3544	27/2756
5	1985	Scottish	BS+(AF)+IMC	57	4531	1979	0	54/3511	30/2999
6	1985	West Midlands UK	B+S+AF+IMC	59	4957	2164	25	81/3976	56/3170
7	1986	CRC, UK	Various	58	3616	570	0	37/2213	42/1973
8	1987	INT Milan 3	†B+S	52	4429	2146	0	29/3631	28/2944
9	1989	NSABP B-21	†B+S	59	5394	739	0	39/3163	28/2970
10	1990	Tampere Finland	B	56	2181	484	0	7/1505	14/1160
11	1991	GBSG V Germany	B+S	60	1766	0	0	6/976	6/790
12,13	1991	SweBCG 91-RT	B	60	9840	2064	0	94/6214	80/5690
14,15	1992	PMH Toronto	†B+S	68	5085	114	0	25/2702	21/2497
16	1992	BASO II	†Various	57	2999	53	0	4/1567	8/1485
17	1994	CALGB 9343	†B	76	4006	9	0	78/2042	68/1973
18	1996	Austrian BCSG VIIIa	†B+(S)	65	4598	14	0	19/2356	22/2256
19	1999	PRIME I	†B	71	1024	0	0	10/505	10/519
20	2000	RT55-75 Maugeri Italy	†B+S	65	3045	0	0	7/1531	3/1514

Table S3 contd. Trials included, regions irradiated, median age at entry, distribution of woman-years since entry and, in each trial arm (RT or No RT), numbers of deaths without breast cancer recurrence and woman-years.

AF=axilla and/or supraclavicular fossa, B=breast, BCS=breast conserving surgery, CW=chest wall, IMC=internal mammary chain, RT=radiotherapy, S= boost to scar. Parentheses indicate only some women received radiotherapy to this region. * For balance, control patients in 3-way trials or trial strata count twice in totals of deaths/women. † Same polychemotherapy and/or tamoxifen in each trial arm.

Trial reference, type, year started, and name			Regions irradiated	Median age	Woman-years since entry			Deaths without recurrence /woman-years	
					<10	10-19	20+	RT	No RT
Mastectomy with axillary dissection: RT vs not									
21	1961	NSABP B-03*	AF+IMC	58	5318	1821	193	118/3669	136/3663
22	1962	Berlin-Buch ABC	CW+AF+IMC	59	1365	380	2	38/831	26/916
23	1964	Oslo X-ray	CW+AF	52	4226	2756	2459	124/4850	110/4591
23	1964	Oslo Co-60	AF+IMC	54	4398	2920	1811	140/4292	108/4837
24	1969	Heidelberg XRT	AF+IMC	60	797	314	0	33/624	17/487
25,26	1971	Stockholm A*	CW+AF+(IMC)	55	8565	5334	3393	195/9633	156/7659
-	1971	SASIB	(CW)+AF+IMC	52	1519	124	75	10/914	3/804
27,28	1973	Mayo 70-56-32	†(CW)+AF+IMC	55	1339	679	310	20/1195	15/1133
29	1973	INT Milan 1	AF+IMC	50	131	88	92	2/183	1/128
30	1974	DFCI Boston	†CW+AF	51	1083	158	0	11/610	2/631
31	1974	Piedmont OA	†(CW)+AF+IMC	53	1726	231	0	11/966	8/991
32	1976	SECSG 1	†CW+AF+IMC	52	1026	78	0	6/570	4/534
33	1976	Glasgow	†CW+AF+IMC	54	1166	377	2	14/838	14/707
34	1977	MD Ander. 7730B	†CW+S+AF+IMC	50	569	231	0	1/299	0/501
35	1978	S Sweden II:1	†CW+AF+IMC	58	5103	2082	386	87/3723	74/3848
-	1978	Toronto-Edmont.	†AF+IMC	43	310	122	1	1/243	0/190
36	1978	BCCA Vancouver	†CW+AF+IMC	44	2030	1135	162	10/1933	4/1394
37	1978	Düsseldorf U.	†CW+AF+IMC	47	291	0	0	3/95	10/196
38	1979	Coimbra	†CW+AF+IMC	53	628	143	0	10/422	6/349
39	1979	Metaxas Athens	†CW+AF+IMC	54	398	101	3	1/250	0/252
40	1980	Helsinki	†CW+AF+IMC	52	609	103	0	2/315	5/397
41	1980	NSABC Israel	†CW+AF+IMC	52	799	174	0	2/477	0/496
42,43	1982	DBCG 82b premenop.	†CW+AF+IMC	46	10451	5081	158	52/8758	32/6932
43,44	1982	DBCG 82c postmenop.	†CW+AF+IMC	62	7819	2812	80	98/5863	96/4848
45	1982	ECOG EST3181	†CW+AF+IMC	52	1724	714	4	16/1225	21/1217
46	1984	GBSG 03 Germany	†CW+AF+IMC	55	1190	109	0	11/676	4/623
Mastectomy with axillary sampling: RT vs not									
47	1973	Southampton UK	CW+AF+IMC	54	886	517	203	18/907	10/699
48	1974	Edinburgh I	CW+AF+IMC	53	2433	1525	979	62/2573	45/2364
49	1985	Nottingham	CW+AF	60	295	24	0	1/192	2/127
7	1986	CRC, UK	Various	58	449	53	0	4/253	7/249
Mastectomy alone: RT vs not									
50	1970	Manchester RBS1	CW+AF+IMC	54	4413	2316	215	96/3849	71/3095
51,52	1970	Kings/Cambridge	CW+AF+IMC	54	16970	6892	1671	285/13167	233/12366
53	1971	NSABP B-04	CW+AF+IMC	55	4417	2187	792	110/3968	85/3428
54	1978	Scottish D	†CW+AF+IMC	59	619	337	47	8/486	10/517
55	1985	Tokyo CIH PS	†AF+IMC	48	495	29	0	2/264	2/260
55	1988	Tokyo CIH N2	†AF+IMC	50	383	6	0	1/200	1/189

Table S3 contd. Trials included, regions irradiated, median age at entry, distribution of woman-years since entry and, in each trial arm (RT or No RT), numbers of deaths without breast cancer recurrence and woman-years.

AF=axilla and/or supraclavicular fossa, B=breast, BCS=breast conserving surgery, CW=chest wall, IMC=internal mammary chain, RT=radiotherapy, S= boost to scar. Parentheses indicate only some women received radiotherapy to this region. * For balance, control patients in 3-way trials or trial strata count twice in totals of deaths/women. † Same polychemotherapy and/or tamoxifen in each trial arm.

Trial reference, type, year started, and name			Regions irradiated	Median age	Woman-years since entry			Deaths without recurrence /woman-years	
					<10	10-19	20+	RT	No RT
RT vs nodal surgery									
56	1951	Copenhagen BCT	CW+AF+IMC	58	3048	1555	1404	102/2969	103/3038
57	1964	SE Scotland	CW+AF+IMC	55	3734	2197	1697	96/3382	107/4246
50	1970	Manchester RBS2	CW+AF+IMC	57	1449	604	62	30/1116	26/999
53	1971	NSABP B-04	CW+AF+IMC	55	7721	3506	1214	177/6061	174/6380
-	1972	WSSA Glasgow	CW+AF	55	1126	5	0	12/530	9/601
-	1972	CMN Mexico	Unknown	48	1599	227	0	8/957	3/869
-	1976	Berlin-Buch	IMC Peripheral	52	743	50	0	5/434	5/359
58	1980	Edinburgh	CW+AF+IMC	57	1033	453	0	13/838	10/648
59	1982	Ins.Curie Paris	†B+(AF)+(IMC)	51	5288	2781	153	25/4123	26/4099
BCS alone + RT vs mastectomy + axillary dissection									
60	1961	Guy's London	†B+AF+IMC	58	4012	2073	1031	82/2928	112/4188
BCS + RT vs mastectomy, both with axillary dissection									
61	1972	IGR Villejuif	B+(AF)+IMC	52	1411	896	222	11/1319	15/1210
29,62	1973	INT Milan 1	†B+(AF)+IMC	50	5795	3991	2653	78/6187	88/6252
1	1976	NSABP B-06	B	51	9387	5587	1217	115/7965	102/8226
63,64	1979	NCI Bethesda	†B+(AF)+(IMC)	50	1781	1030	83	15/1360	15/1534
65	1980	EORTC 10801	B+(AF)+(IMC)	53	6193	1524	0	20/3900	26/3817
66	1983	Danish BCG 82TM	B	51	4119	2583	66	21/3574	25/3194
67	1984	GBSG 01 Germany	B+(F)+IMC	56	506	86	0	5/251	5/341
Ductal carcinoma in situ: RT vs no RT									
68	1985	NSABP B-17	B+(S)	55	6364	3000	13	51/5031	44/4346
69	1986	EORTC 10853	B+(S)	53	7862	1111	0	14/4627	8/4346
70	1987	SweDCIS	B	56	6904	667	0	39/4007	37/3564
71	1990	UK/ANZ DCIS	†B	56	4355	0	0	8/2216	6/2139

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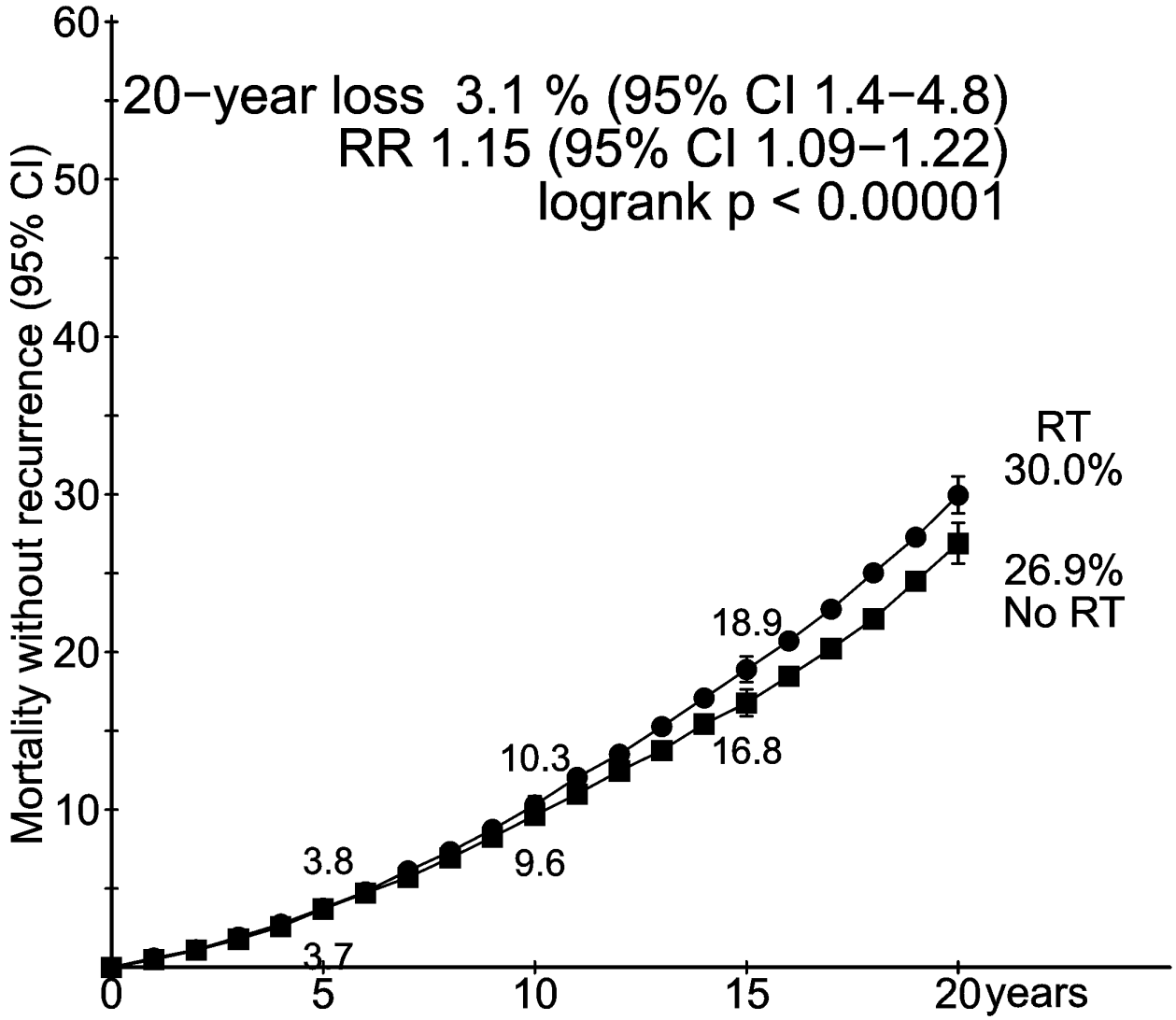
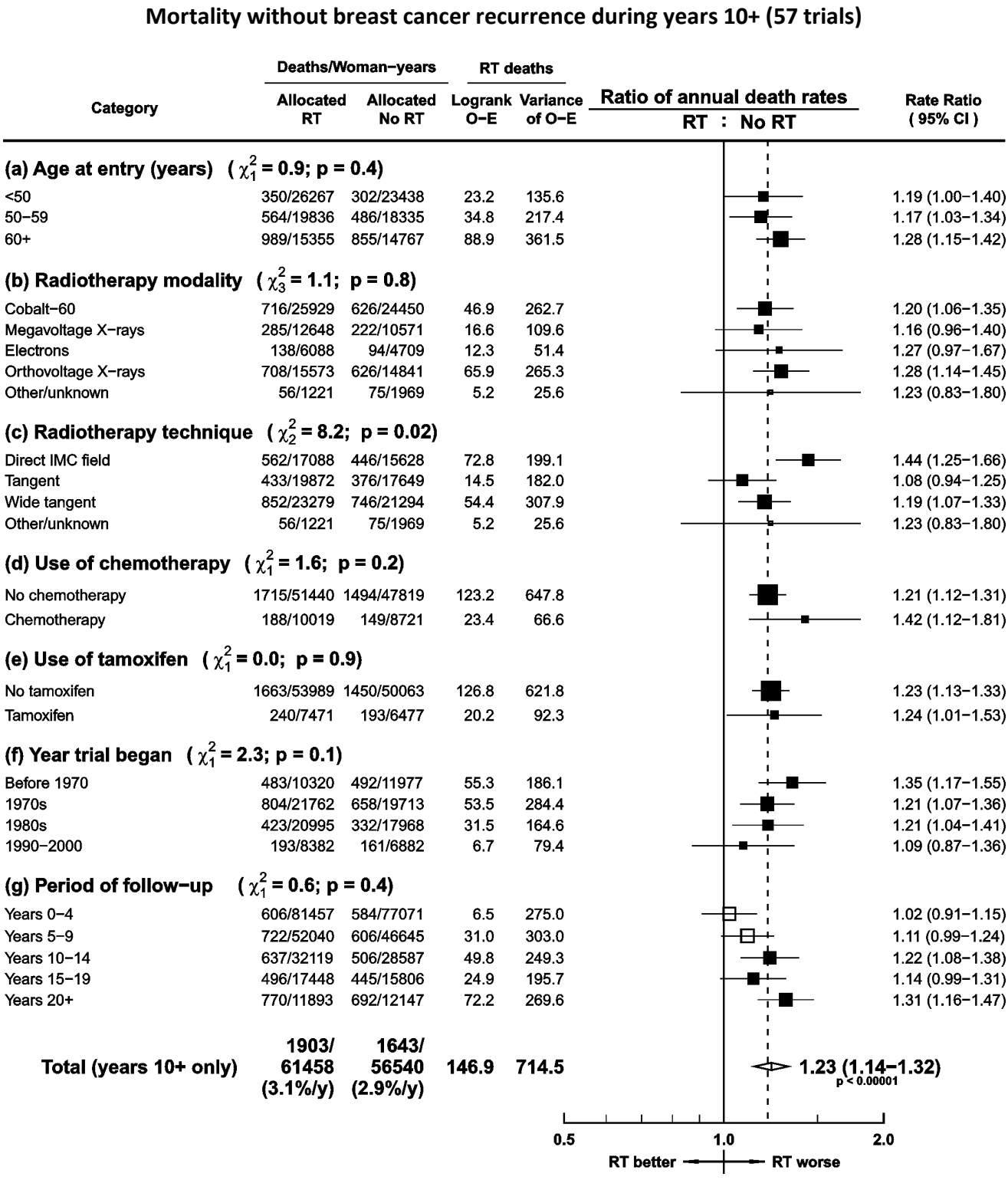
Figure S1. Effect of allocation to radiotherapy (RT) on mortality without breast cancer recurrence.



Mortality without recurrence rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15−19	Years 20+
RT	0.74 (606/81457)	1.39 (722/52040)	1.98 (637/32119)	2.84 (496/17448)	6.47 (770/11893)
No RT	0.74 (553/75003)	1.28 (581/45360)	1.74 (483/27681)	2.79 (423/15138)	5.67 (647/11413)
Rate ratio, from	1.02 (0.91−1.15)	1.11 (0.99−1.24)	1.22 (1.08−1.38)	1.14 (0.99−1.31)	1.31 (1.16−1.47)
(O−E)/V	6.5/275.0	31.0/303.0	49.8/249.3	24.9/195.7	72.2/269.6

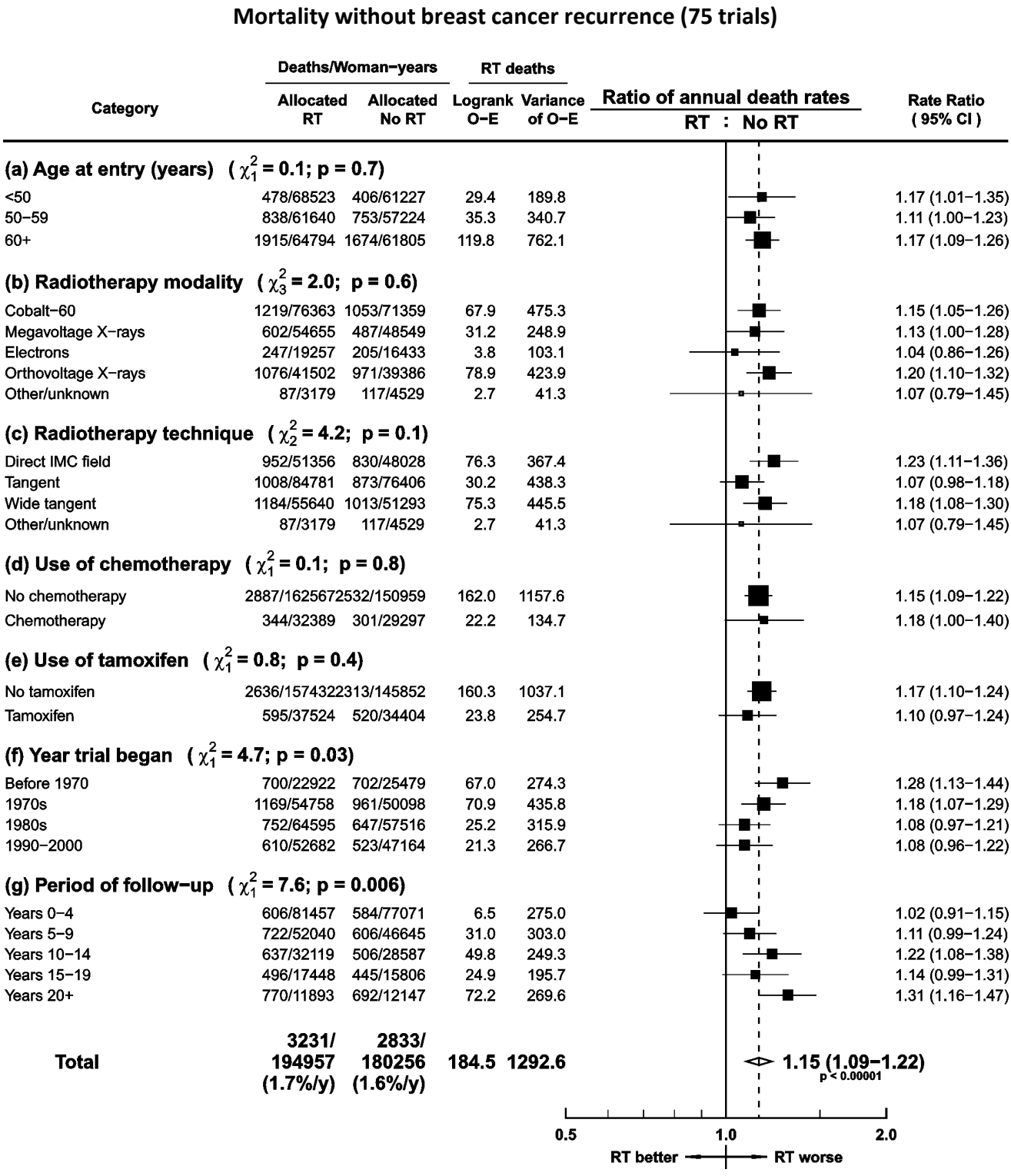
Figure S2. Effect of allocation to radiotherapy on mortality without breast cancer recurrence during years 10+.



Areas of squares are proportional to amounts of information, open boxes do not contribute to test for trend.

IMC=internal mammary chain.

Figure S3. Effect of allocation to radiotherapy on mortality without breast cancer recurrence (all years).



Areas of squares are proportional to amounts of information.

IMC=internal mammary chain.

Table S4. Effect of allocation to radiotherapy (RT) on non-breast-cancer mortality without any breast cancer recurrence. DVT= deep vein thrombosis, COPD=chronic obstructive pulmonary disease

	Number of deaths (total woman-years)			Logrank statistics			
	RT (194957)	No RT (180250)	Adjusted excess* (95% CI)	O-E	V	Rate ratio (95% CI)	P Value
Cancers							
Leukaemia	20	19	0 (-12-11)	-0.2	8.6	0.97 (0.50—1.91)	0.94
Lung	120	65	43 (17-69)	21.6	43.5	1.64 (1.22—2.21)	0.001
Pleura	2	0	-	0.6	0.4	-	0.36
Oesophagus	17	6	10 (1-19)	5.0	5.5	2.51 (1.08—5.72)	0.03
Pancreas	36	25	10 (-4-24)	5.0	12.9	1.47 (0.85—2.54)	0.16
Stomach	36	36	-3 (-19-12)	-1.7	16.3	0.90 (0.55—1.46)	0.68
Large intestine	64	59	2 (-19-22)	0.9	27.6	1.03 (0.71—1.50)	0.87
Ovary	39	41	-5 (-22-12)	-2.6	18.9	0.87 (0.56—1.37)	0.55
Endometrium	18	14	3 (-8-13)	1.3	7.7	1.18 (0.58—2.40)	0.64
Cervix	9	10	-2 (-10-7)	-0.9	4.7	0.83 (0.33—2.04)	0.69
Melanoma	2	1	-	0.7	0.7	-	0.38
Soft tissue	7	4	3 (-3-9)	1.3	2.4	1.75 (0.49—6.09)	0.39
Lymphoma	32	19	9 (-4-23)	4.6	12.0	1.46 (0.83—2.58)	0.19
Other specified site	73	76	-5 (-27-18)	-2.3	32.6	0.93 (0.66—1.31)	0.69
Circulatory							
Ischaemic heart disease	368	296	66 (19-114)	33.2	146.2	1.26 (1.07—1.48)	0.006
Arrhythmia	42	19	22 (7-36)	10.8	14.2	2.14 (1.27—3.60)	0.004
Heart failure, with IHD	14	12	2 (-8-11)	0.9	6.1	1.16 (0.52—2.56)	0.72
Heart failure, no IHD	63	33	28 (10-46)	14.1	21.2	1.94 (1.27—2.98)	0.002
Heart valve disease	31	15	14 (1-26)	6.9	10.1	1.97 (1.07—3.67)	0.03
Pericardial disease	4	0	-	1.8	1.0	-	0.07
Other heart disease	183	173	7 (-26-42)	3.9	76.8	1.05 (0.84—1.32)	0.66
Pulmonary embolism inc. DVT	32	14	14 (2-27)	7.2	9.8	2.10 (1.11—3.90)	0.02
Stroke	183	175	13 (-22-48)	6.4	80.8	1.08 (0.87—1.35)	0.48
Other specified cause							
External cause	41	36	5 (-12-21)	2.3	17.4	1.14 (0.71—1.83)	0.58
Hepatic	18	17	-1 (-12-10)	-0.6	8.2	0.93 (0.47—1.84)	0.84
Infectious/parasitic	13	5	7 (-1-15)	3.5	4.0	2.36 (0.90—6.39)	0.08
Pneumonia	77	72	11 (-12-33)	5.3	32.7	1.18 (0.83—1.66)	0.35
COPD	28	40	-18 (-34--3)	-9.1	15.6	0.56 (0.34—0.92)	0.02
Other respiratory	34	23	11 (-3-24)	5.3	12.3	1.55 (0.88—2.69)	0.13
Other specified cause	212	247	-34 (-73-5)	-17.0	100.2	0.84 (0.69—1.03)	0.09
Not specified cause							
Unspecified, but not breast	694	626	74 (8-139)	36.9	285.6	1.14 (1.01—1.20)	0.03
Unknown cause	719	655	79 (12-146)	39.4	291.6	1.14 (1.02—1.28)	0.02
All causes	**3231**	**2833**	**369 (228-510)**	**184.4**	**1292.6**	**1.15 (1.09—1.22)**	**<0.0001**

*The adjusted excess number of events (or deaths) in the RT group is calculated as twice the logrank Observed minus Expected (see Methods S1 for details) and allows for RT delaying recurrence. Table S2 relates ICD-10 codes used in grouping diseases.

Table S5. Rates of various types of breast cancer event in women allocated no radiotherapy, by nodal status in the present study.

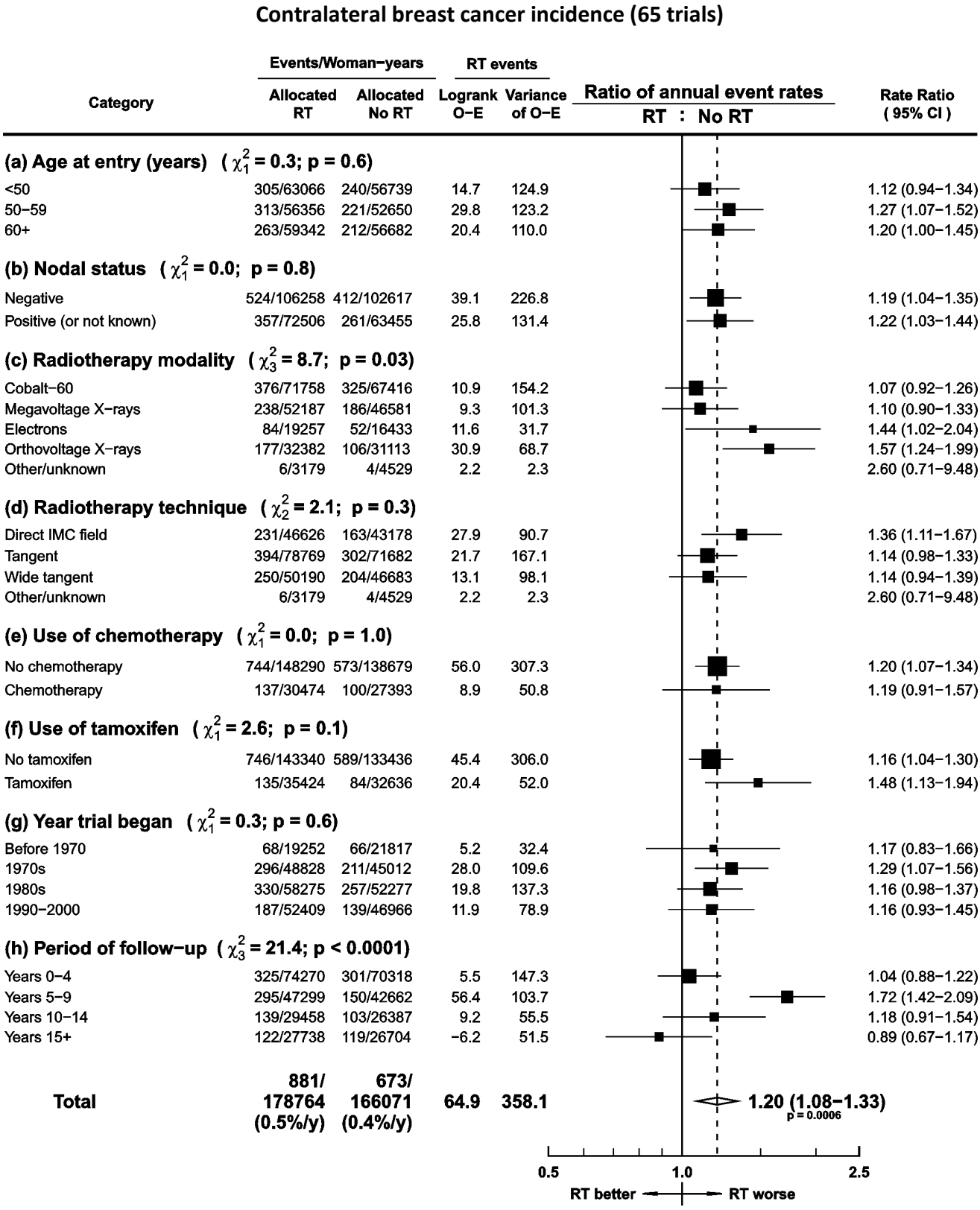
For contralateral breast cancers (column 1 of type of event) the rates are similar in women who were originally treated for node negative and node positive disease. In contrast, for recurrence (columns 2 and 3) the rates are much higher for women who were originally treated for node positive disease. So, the contralateral breast cancers are likely to be new primaries and not wrongly classified recurrent disease.

Nodal status	Type of event					
	Contralateral before any recurrence		**Distant recurrence** as first event		**Any first recurrence** (local or distant)	
	Events /woman-years	**Rate (%/y)**	**Events /woman-years**	**Rate (%/y)**	**Events /woman-years**	**Rate (%/y)**
N0/N-	412/102617	0.40	1633/106871	1.53	3756/114705	3.27
N+/N?	261/63455	0.41	2654/69236	3.83	5076/73972	6.86

75 trials contributed events to this analysis.

Abbreviations: N0=node-negative (pathological), N-= node-negative (clinical or other), N+=node-positive (pathological or clinical), N?-= unknown nodal status.

Figure S4. Effect of allocation to radiotherapy on incidence of contralateral breast cancer.



Areas of squares are proportional to amounts of information.

IMC=internal mammary chain

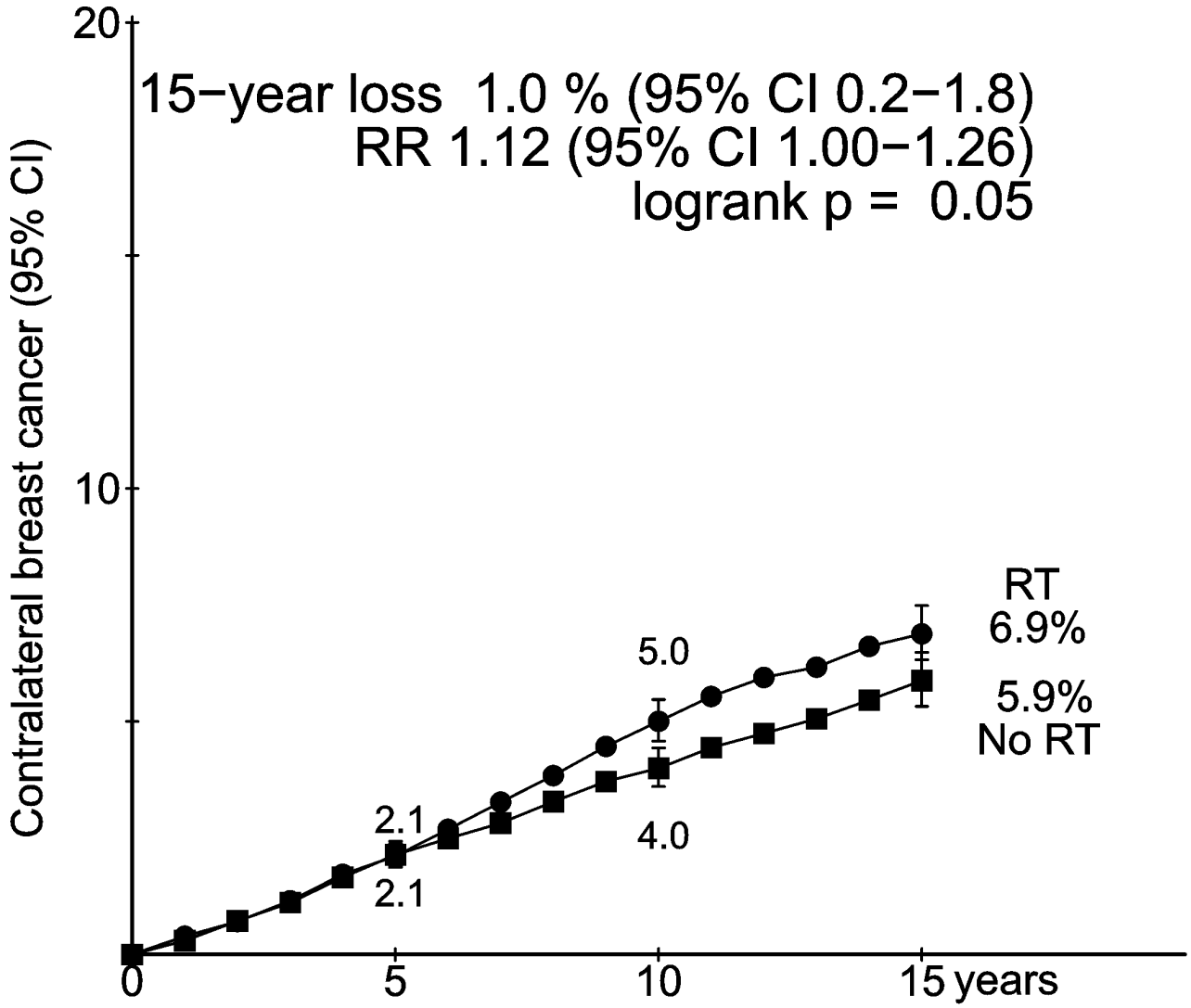
Table S6. Relative risks of contralateral breast cancer after breast cancer radiotherapy in the Surveillance, Epidemiology and End Result (SEER) program and in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) trials, both by time since irradiation.

Period of follow-up (years)	SEER* RT vs no RT Rate ratio (95% CI)	EBCTCG RT vs no RT Rate Ratio (95% CI)
0-4	1.10 (1.05 – 1.16)	1.04 (0.88 – 1.22)
5-9	1.33 (1.24 – 1.42)	1.72 (1.42 – 2.09)
10-14	1.50 (1.36 – 1.65)	1.18 (0.91 – 1.54)
15+	1.37 (1.20 – 1.58)	0.89 (0.67 – 1.17)
All years	1.25 (1.21 – 1.30)	1.20 (1.08 – 1.33)

SEER data based on 13,428 events in 322,863 women. 65 EBCTCG trials contributed events to this analysis (1554 events in 344,829 woman-years).

*The ratio of observed/expected events was calculated for subsequent breast cancer after previous treatment of breast cancer with or without radiotherapy. Observed events were calculated as all second and later (third, fourth, etc) invasive breast cancers that developed at least two months after the first primary cancer was treated, so as to be comparable with the expected numbers derived from baseline SEER incidence rates, which include multiple second tumours. Source: Tables 7.1.8 -11 of Curtis RE, Ron E, Hankey BF, Hoover RN. Chapter 7. New malignancies following breast cancer from: Curtis RE, Freedman DM, Ron E, Ries LAG, Hacker DG, Edwards BK, Tucker MA, Fraumeni JF Jr. (eds). New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. National Cancer Institute, NIH Publ. No. 05-5302. Bethesda, MD, 2006.

Figure S5. Effect of allocation to radiotherapy on contralateral breast cancer. The plot excludes trials of orthovoltage radiotherapy.



Contralateral breast cancer rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	0.43 (266/62179)	0.61 (241/39520)	0.44 (105/24084)	0.45 (92/20599)
No RT	0.42 (244/57665)	0.38 (132/34537)	0.39 (81/20648)	0.44 (81/18279)
Rate ratio, from	1.00 (0.83−1.19)	1.56 (1.26−1.92)	1.04 (0.77−1.40)	0.86 (0.63−1.18)
(O−E)/V	−0.5/122.0	38.5/86.8	1.7/42.8	−5.7/37.8

Table S7. Rate of lung cancer incidence, in women allocated no radiotherapy, compared to various types of breast cancer event, by nodal status in the present study.

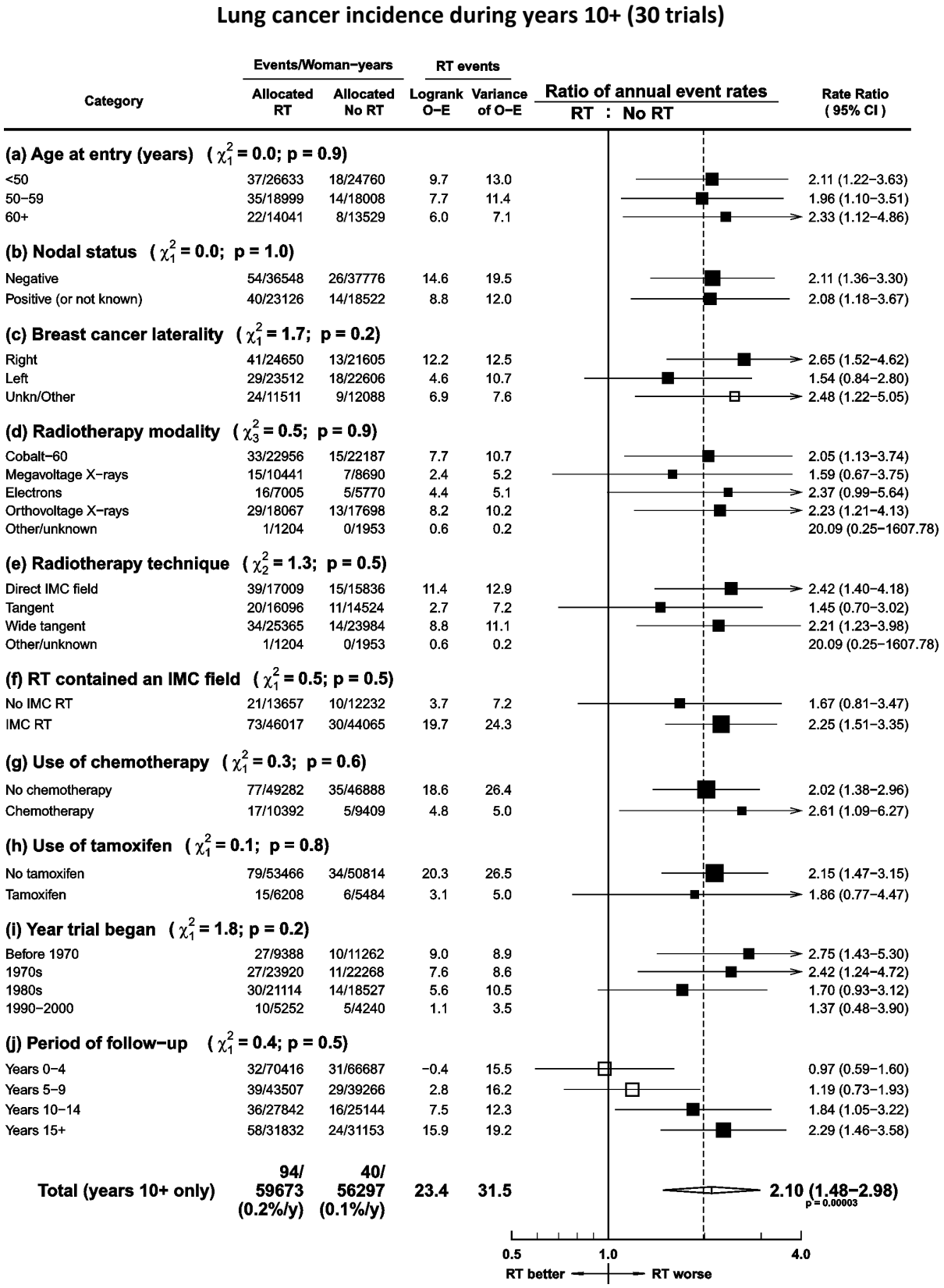
For lung cancers (column 1 of type of event) the rates are similar in women who were originally treated for node negative and node positive disease. In contrast, for recurrence (columns 2 and 3) the rates are much higher for women who were originally treated for node positive disease. So, the lung cancers are likely to be new primaries and not wrongly classified lung metastases.

Nodal status	Type of event					
	Lung cancer (second primary)		**Distant recurrence** as first event		**Any first recurrence** (local or distant)	
	Events /woman-years	**Rate (%/y)**	**Events /woman-years**	**Rate (%/y)**	**Events /woman-years**	**Rate (%/y)**
N0/N-	66/102391	0.06	1633/106871	1.53	3756/114705	3.27
N+/N?	34/59860	0.06	2654/69236	3.83	5076/73972	6.86

75 trials contributed events to this analysis.

Abbreviations: N0=node-negative (pathological), N-= node-negative (clinical or other), N+=node-positive (pathological or clinical), N?-= unknown nodal status.

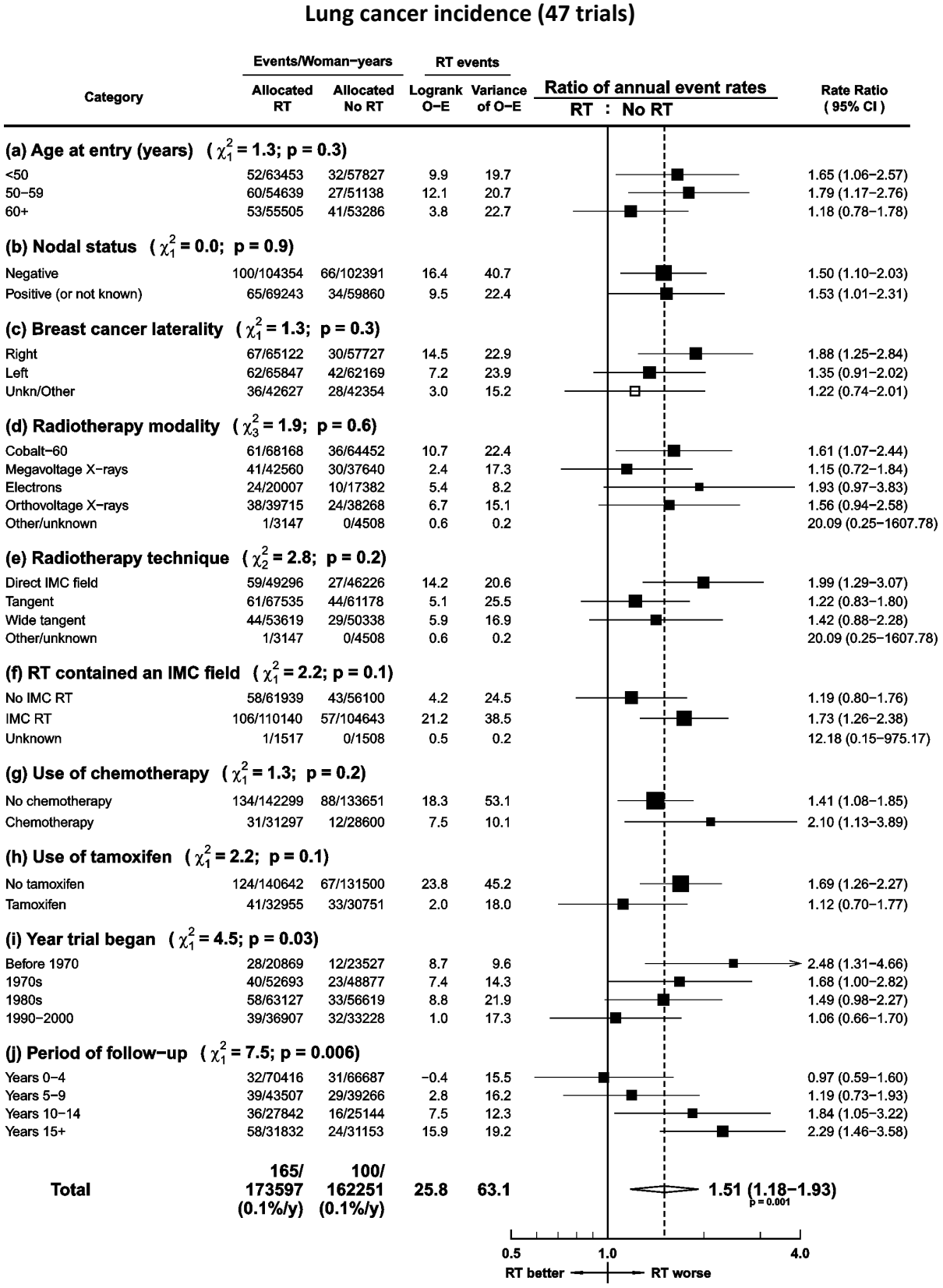
Figure S6. Effect of allocation to radiotherapy on lung cancer incidence during years 10+.



Areas of squares are proportional to amounts of information, open boxes do not contribute to tests for trend or heterogeneity.

IMC=internal mammary chain.

Figure S7. Effect of allocation to radiotherapy on lung cancer incidence (all years).



Areas of squares are proportional to amounts of information, open boxes do not contribute to test for heterogeneity.

IMC=internal mammary chain.

Table S8. Unilateral breast cancer treated with radiotherapy: subsequent incidence of primary lung cancer, ipsilateral vs contralateral, by decade of breast cancer diagnosis and time since diagnosis, for women in the Surveillance, Epidemiology and End Result (SEER) program.

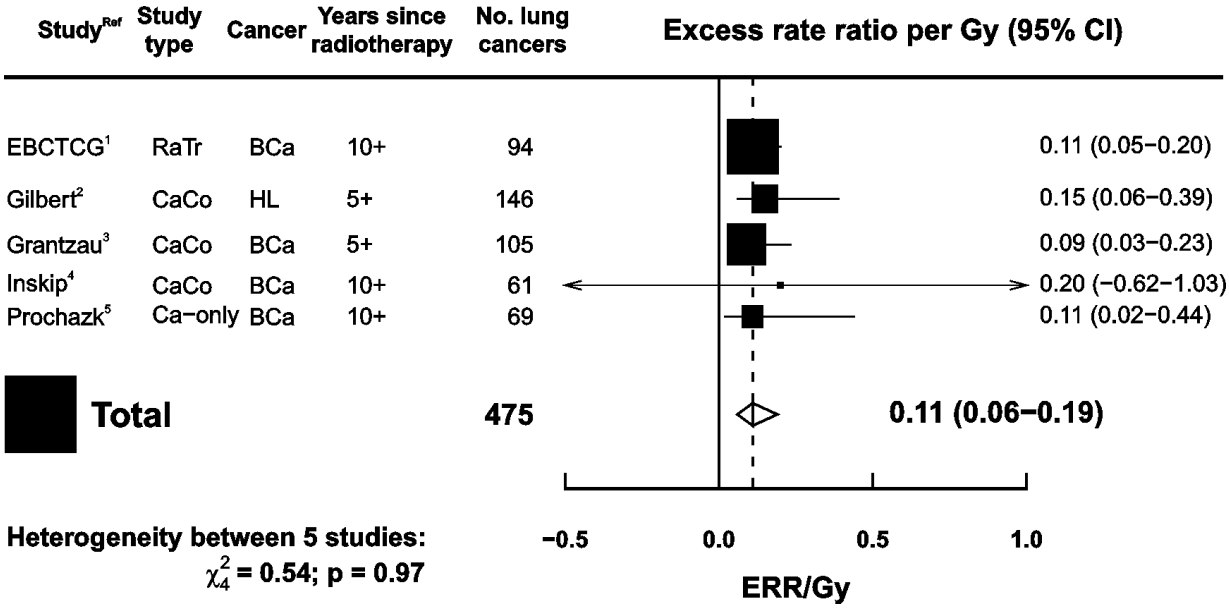
Unilateral local or regional breast cancer treated with radiotherapy		Incidence of new primary lung cancer ipsilateral/contralateral to irradiated breast	
Decade of breast cancer diagnosis	**Years since breast cancer diagnosis**	**Number of lung cancers**	**Rate ratio (and 95% CI)**
1970s	<10 years	26/40	0.65 (0.40-1.07)
	10-19 years	66/31	2.13 (1.39-3.26)
	20+ years	68/27	2.52 (1.61-3.93)
1980s	<10 years	107/112	0.96 (0.73-1.25)
	10-19 years	160/99	1.62 (1.26-2.08)
	20+ years	101/48	2.10 (1.49-2.97)
1990s	<10 years	481/434	1.11 (0.97-1.26)
	10-19 years	377/294	1.28 (1.10-1.49)
	20+ years	22/10	2.20 (1.04-4.65)
2000s	<10 years	1237/1232	1.00 (0.93-1.09)
	10-14 years	128/96	1.33 (1.02-1.74)
	15+ years	-	-
1973-2013	<10 years	1851/1818	1.02 (0.95-1.09)
	10-19 years	731/520	1.41 (1.26-1.57)
	20+ years	191/85	2.25 (1.74-2.90)

SEER public-use data on 393,338 women diagnosed from 1973 to 2013 with local or regional breast cancer of known laterality that were treated with radiotherapy. Follow-up for first new primary lung cancer, and its laterality, was to 1.1.2014. Rate ratios estimated using Poisson regression with stratification by calendar year of diagnosis, time since diagnosis, age (all in 5-year groups) and race (white, black, other/unknown).

Source of data:

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2013), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the November 2015 submission.

Figure S8. Estimates of excess rate ratio per gray (ERR/Gy) for lung cancer in several epidemiological studies and the present study.



Sizes of the squares are directly proportional to the amount of information each study contains.

This above figure summarises available evidence, from 4 other studies and the current study, for the relationship between radiation dose and subsequent lung cancer. There is very little heterogeniety between the indivudal estimates of the ERR/Gy. The values shown here are for the overall ERR /Gy i.e. smokers and non-smokers together. The RRs per gray in observational studies are based on total events in: 282 ever smokers, 52 non-smokers (two studies included unknown status with non-smokers), and 47 of unknown smoking status. There are not enough events in non-smokers to reliably estimate the ERR/Gy for them separately. However, available evidence suggests that the ERR/Gy may be higher in smokers [Gilbert 2003, Grantzau 2014, Prochazka 2005]. There is no evidence that the dose-response relationship departs from linearity.

Since smoking status was not available, absolute risk estimates from the current study (figure 3) are based on the overall RR in smokers and non-smokers together. If in fact the ERR/Gy is higher in smokers than non-smokers, absolute risks due to radiotherapy in the smokers may be *underestimated*. In contrast absolute risks for non-smokers in the current study may be an *over-estimate* but even then their absolute risk would remain very small (estimate is ~ 0.3% absolute lung cancer mortality increase due to radiotherapy, see figure 3).

BCa=breast cancer, CaCo=case-control, Ca-only=case-only, HL=Hodgkin lymphoma, RaTr=randomised trial.

References

1. EBCTCG: the present study

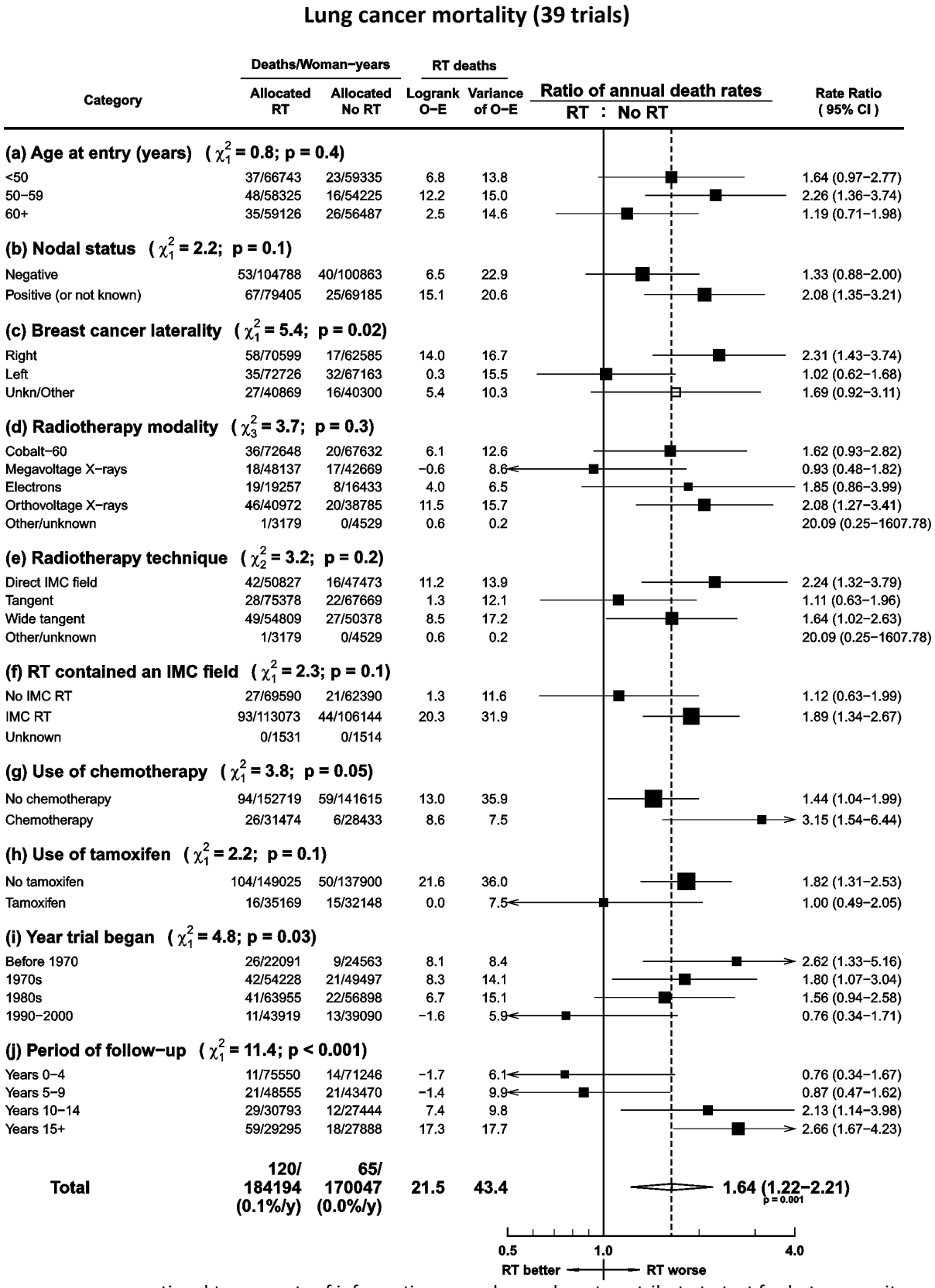
2. Gilbert ES, Stovall M, Gospodarowicz M, et al. Lung cancer after treatment for Hodgkin's disease: Focus on radiation effects. *Radiat Res* 2003; 159: 161-73.

3. Grantzau T, Thomsen MS, Vaeth M, Overgaard J. Risk of second primary lung cancer in women after radiotherapy for breast cancer. *Radioth Oncol* 2014; 111: 366-73.

4. Inskip PD, Stovall M, Flannery JT. Lung cancer risk and radiation dose among women treated for breast cancer. *J Natl Cancer Inst* 1994; 86: 983-988.

5. Prochazka M, Hall P, Gagliardi G, at al. Ionizing radiation and tobacco use increases the risk of a subsequent lung carcinoma in women with breast cancer: Case-only design. *J Clin Oncol* 2005; 23: 7467-74.

Figure S9. Effect of allocation to radiotherapy on lung cancer mortality (all years).



Areas of squares are proportional to amounts of information, open boxes do not contribute to test for heterogeneity.

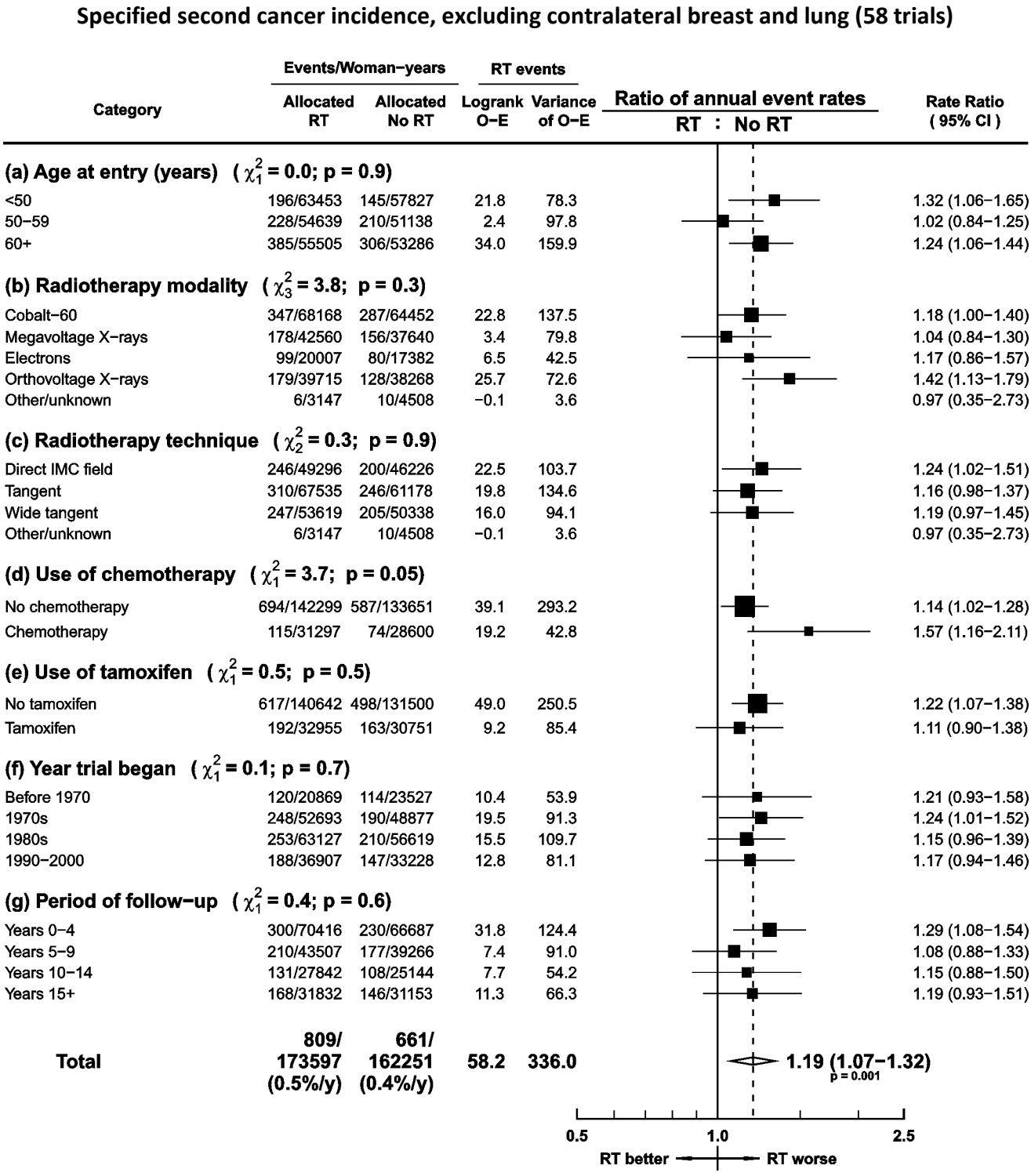
IMC=internal mammary chain.

Table S9: Estimated effect of typical 2010s radiotherapy regimens on mortality from lung cancer by age at irradiation and smoking history

Epidemiological 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 (see Methods S1 for methodology). Estimated risks calculated below are most applicable to an average female smoker in the USA or UK.

	Estimated lung cancer risk by age 80 (%)		
	RT	**No RT**	**Excess from RT**
Radiotherapy at age 50			
Never smoked, or stopped by age 30	0.8	0.5	0.3
Stopped at age 40	1.8	1.2	0.6
Stopped at age 50	3.9	2.6	1.3
Continuing smoker	13.8	9.4	4.4
Radiotherapy at age 60			
Never smoked, or stopped by age 30	0.6	0.4	0.2
Stopped at age 40	1.5	1.1	0.4
Stopped at age 50	3.4	2.4	1.0
Stopped at age 60	6.0	4.4	1.6
Continuing smoker	11.8	8.7	3.1
Radiotherapy at age 70			
Any smoking history	Various	Various	Little excess by 80

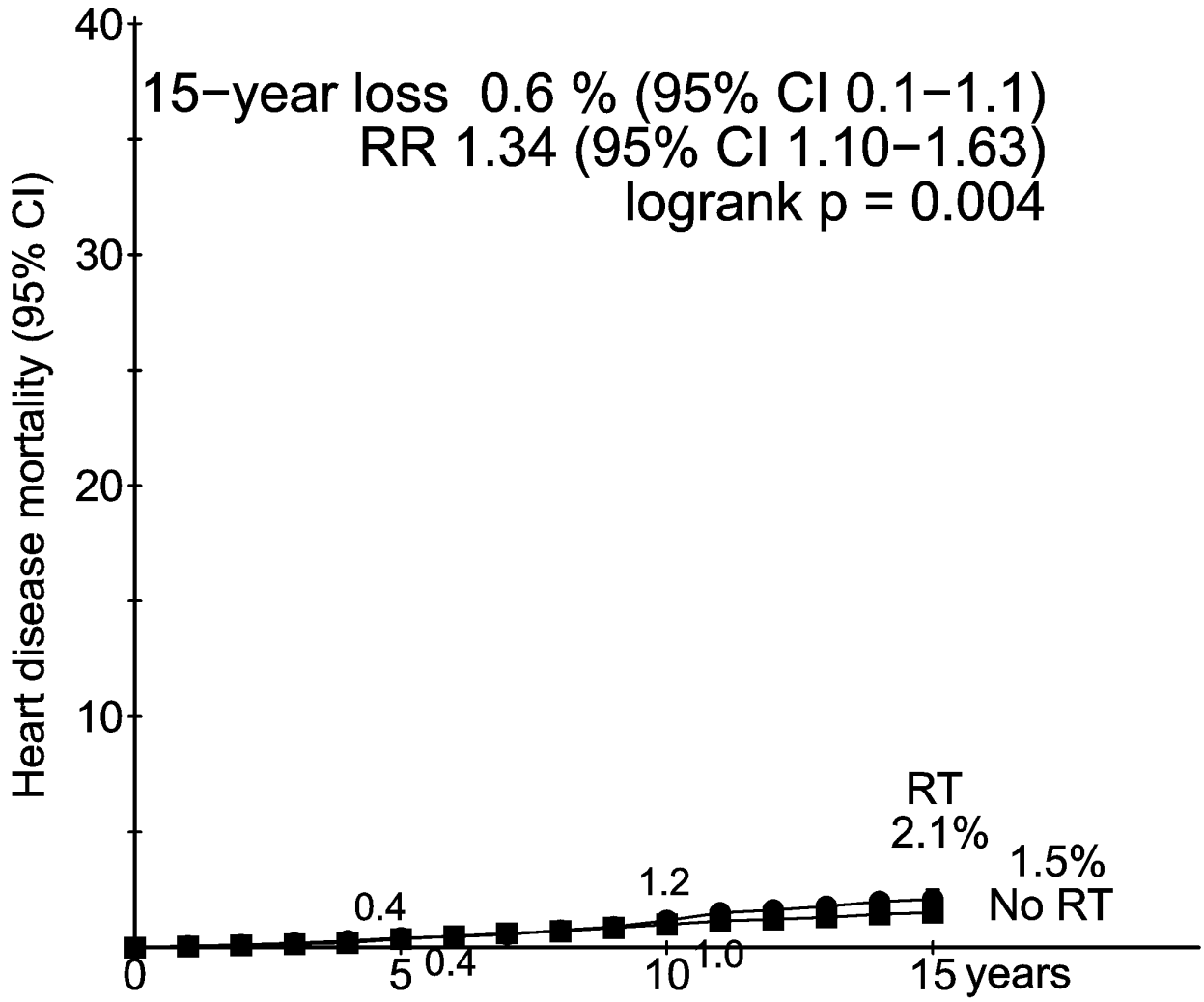
Figure S10. Effect of allocation to radiotherapy on specified second cancer incidence (excluding contralateral breast and lung).



Areas of squares are proportional to amounts of information.

IMC=internal mammary chain.

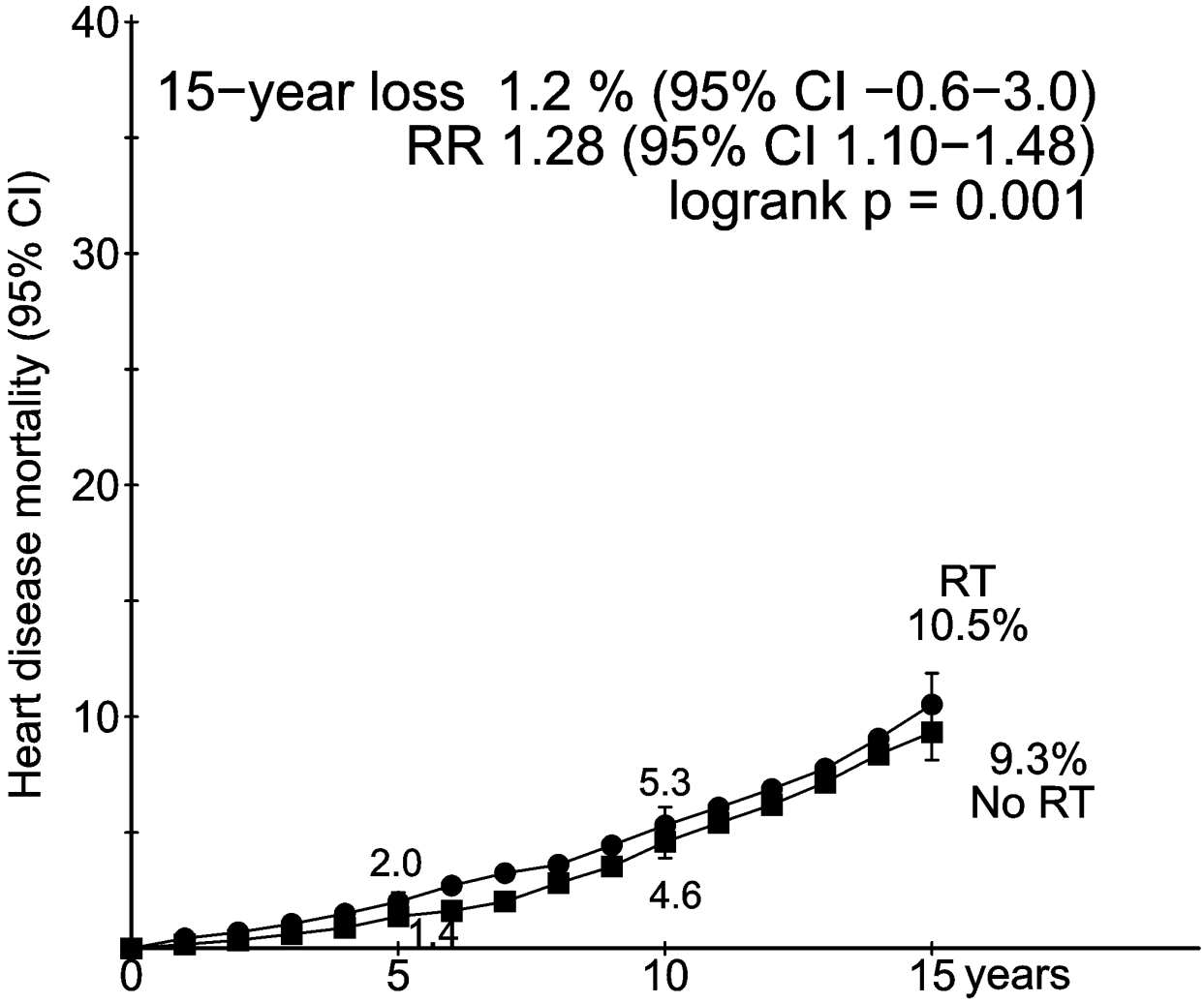
Figure S11. Effect of allocation to radiotherapy (RT) on heart disease mortality in the trials for women aged <60 years at entry: absolute risk nowadays will be lower in populations with lower background rates.



Heart disease mortality rates (%/year) and logrank analyses

	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	0.08 (38/47378)	0.14 (46/32317)	0.19 (43/22137)	0.56 (130/23237)
No RT	0.07 (30/42758)	0.13 (35/27663)	0.11 (20/18726)	0.44 (92/20730)
Rate ratio, from	1.15 (0.71−1.87)	1.15 (0.74−1.79)	1.81 (1.08−3.03)	1.37 (1.03−1.82)
(O−E)/V	2.4/16.6	2.7/19.5	8.6/14.5	15.2/47.9

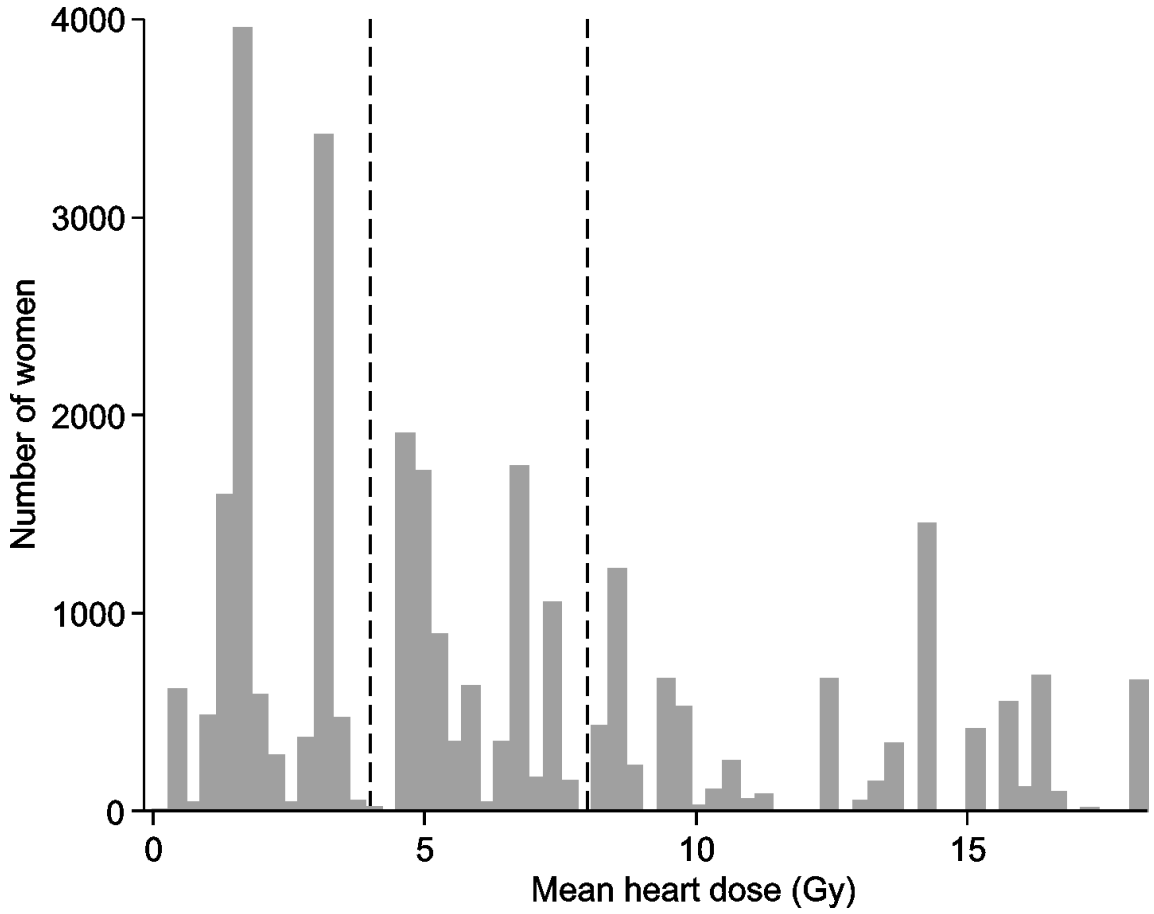
Figure S12. Effect of allocation to radiotherapy (RT) on heart disease mortality in the trials for women aged 60+ years at entry: absolute risk nowadays will be lower in populations with lower background rates.



Heart disease mortality rates (%/year) and logrank analyses

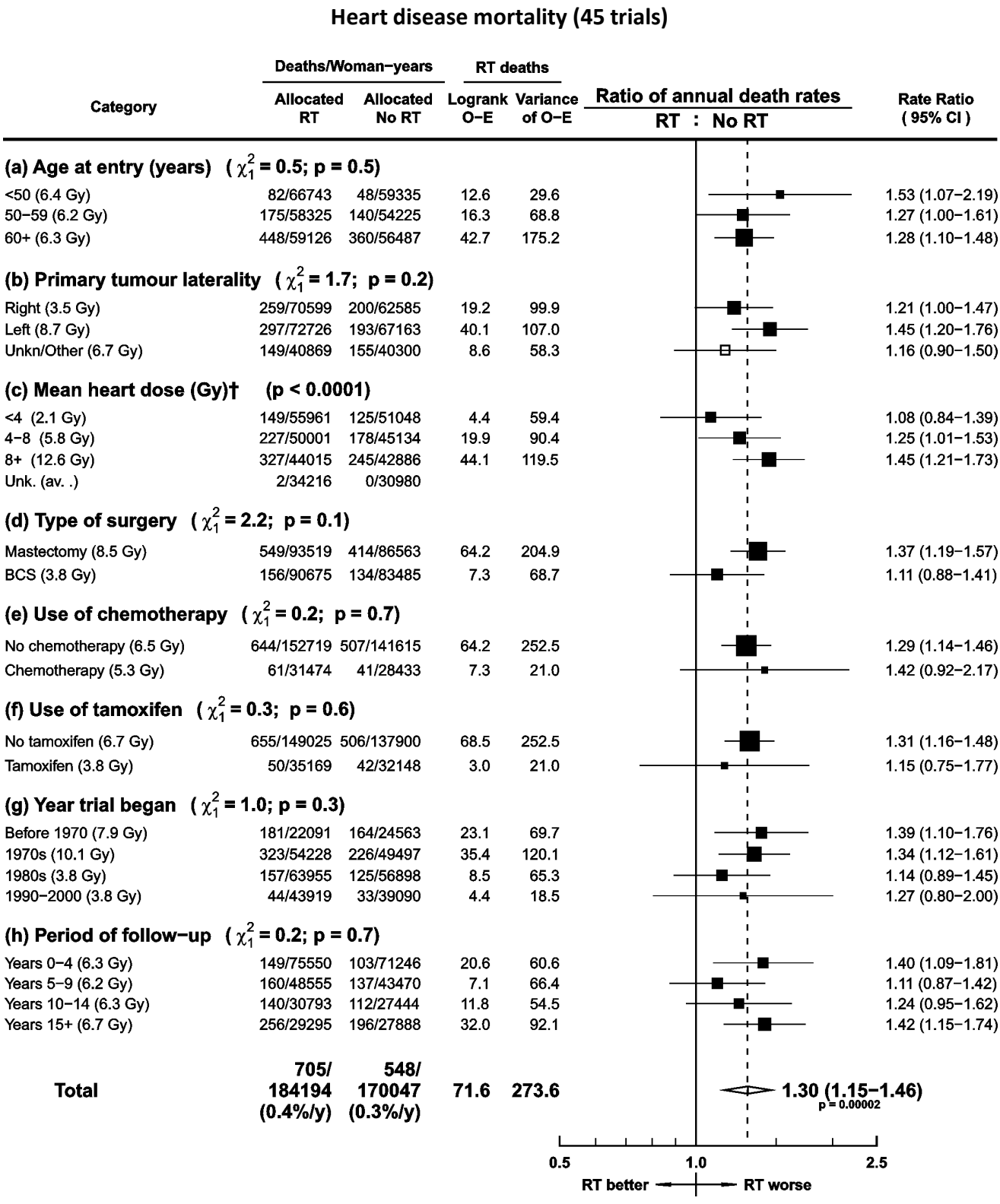
	Years 0−4	Years 5−9	Years 10−14	Years 15+
RT	0.39 (111/28173)	0.70 (114/16239)	1.12 (97/8656)	2.08 (126/6058)
No RT	0.26 (70/26420)	0.63 (91/14523)	1.04 (81/7812)	1.55 (89/5756)
Rate ratio, from	1.51 (1.13−2.03)	1.10 (0.82−1.46)	1.08 (0.79−1.48)	1.46 (1.09−1.97)
(O−E)/V	18.2/44.0	4.4/46.9	3.2/40.0	16.9/44.2

Figure S13. Histogram of estimated mean heart doses for 29,985 women in trials in the present study which contributed to analyses of heart disease mortality. The dashed lines show the category cut-points at 4 Gy & 8 Gy used to create the dose categories in figures 2 and 3.



Note: Trials which either did not supply cause-specific mortality or recorded no heart disease deaths are excluded from the histogram.

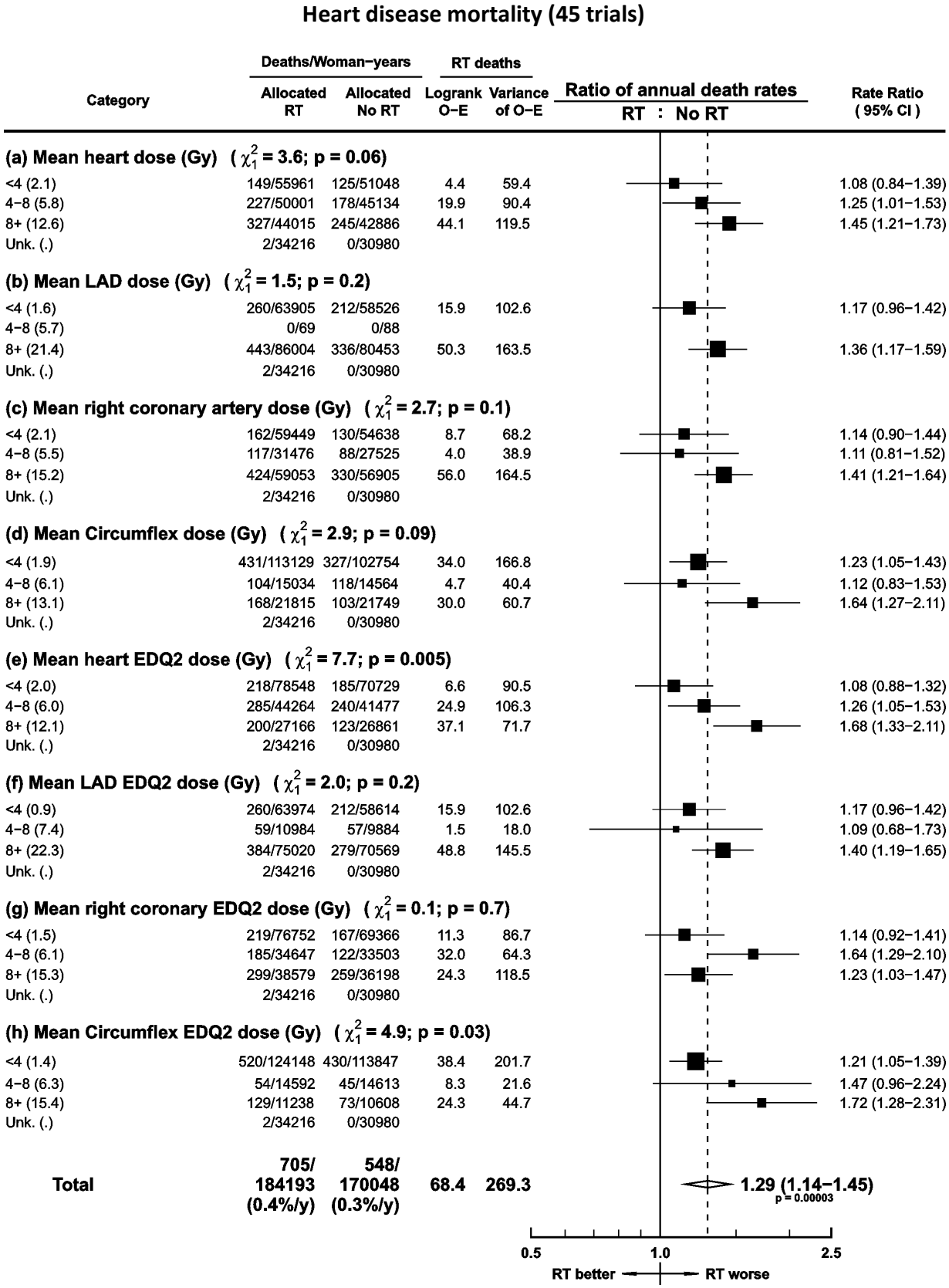
Figure S14a. Effect of allocation to radiotherapy on mortality from heart disease.



Areas of squares are proportional to amounts of information, open boxes do not contribute to test for heterogeneity.

† Test for trend through zero effect at zero dose.

Figure S14b. Effect of allocation to radiotherapy on heart disease mortality by different dose measures to various cardiac organs at risk.



Sizes of the squares are directly proportional to the amount of information each category level contains.

The average mean dose is shown for each category level. The average of left and right dose was used for women with unknown laterality. LAD=Left anterior descending coronary artery, EQD2=Equivalent dose in 2 gray fractions.

Figure S14c. **Heart disease mortality rate ratio (RR) by trial-specific mean radiation dose, converted to equivalent mean dose in 2 Gy fractions, to the heart**

The line was estimated using doses for individual women. Squares (with areas proportional to information content) show EQD2 dose categories <4, 4-8, and 8+ Gy, with mean doses 2.0, 6.0, and 12.1 EQD2 Gy.

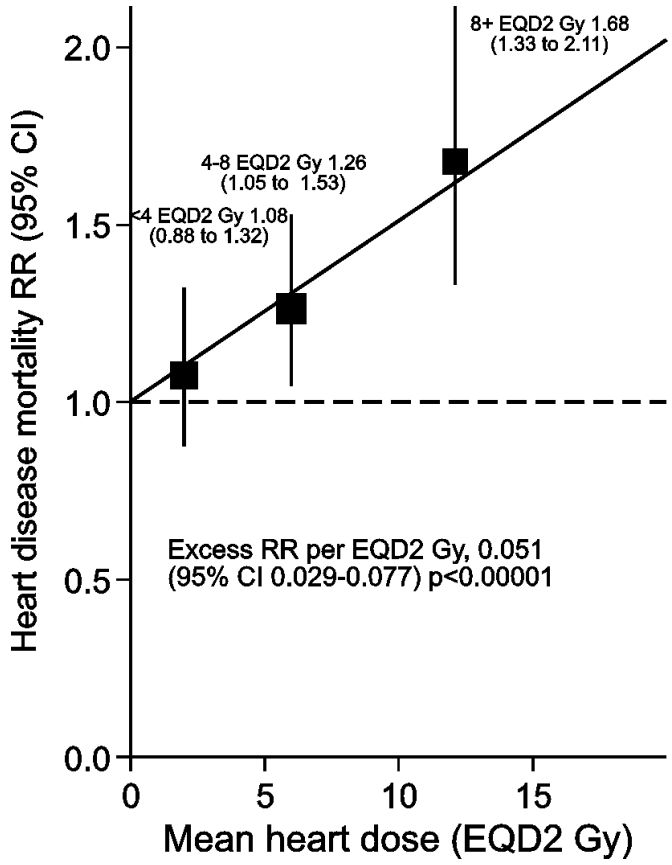
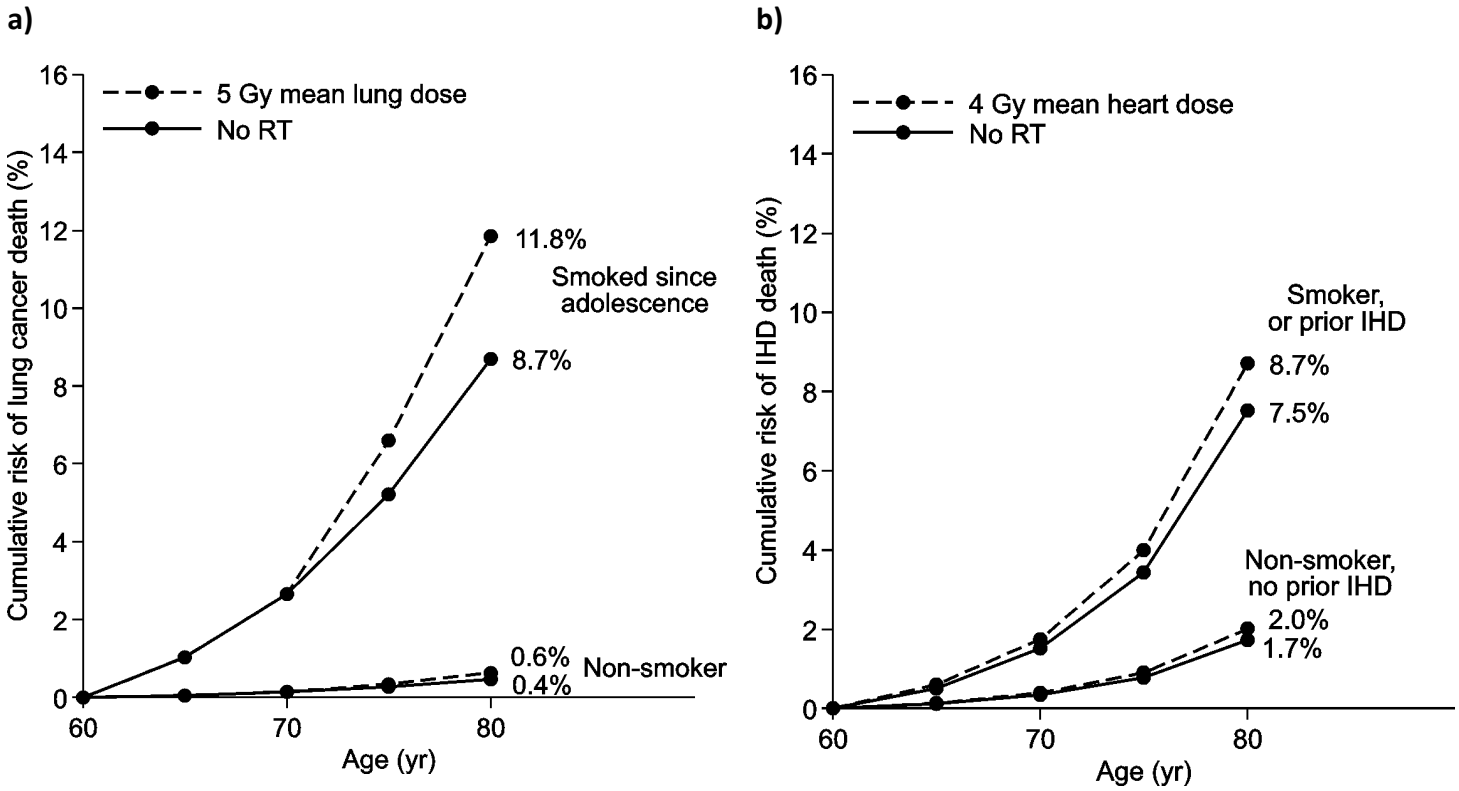


Figure S15. Estimated effects among 60-year-old smokers and non-smokers of typical 2010s radiotherapy regimens on mortality from (a) lung cancer and (b) ischaemic heart disease (IHD)

Epidemiological 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 (see Methods S1 for methodology).



Methods S2. Systematic review of heart and lung doses from breast cancer radiotherapy, 2010-2015

Study identification

Embase and SCOPUS databases were searched to identify publications with the following terms in the title or abstract: dos* AND breast* AND cancer*/carcinom*/tumor*/tumour* AND radiation/radiotherap*. Reference sections of relevant publications were scanned to identify further studies.

Study eligibility criteria

Studies were identified using PRISMA guidelines [PRISMA statement]. Studies published between 1/1/2010-12/31/2015 and reporting whole heart dose (i.e., dose averaged over the whole heart) and/or mean total lung dose, mean ipsilateral lung dose, or mean contralateral lung dose for specific regimens were eligible. Eligibility was not affected by whether the radiotherapy plans were subsequently delivered to patients. Studies reporting heart or lung doses from tumour bed boost radiotherapy alone were excluded.

Data collation

For each regimen in each eligible study, the following quantities were abstracted if available: mean heart dose, mean ipsilateral lung dose, mean contralateral lung dose, mean combined lung dose (ipsilateral and contralateral lungs together).

Calculation of typical 2010s heart dose (see Taylor 2015 for details of methodology)

The typical 2010s heart dose from left breast cancer radiotherapy was calculated as follows. For each regimen, the mean whole heart dose was abstracted i.e. the arithmetic mean of the whole heart doses for the CT plans used for the regimen. Mean whole heart dose was reported for 525 left radiotherapy regimens, and the average of these 525 doses was 5.2 Gy (IQR 1.9-7.4).

The typical 2010s heart dose from right-sided regimens was calculated in the same way. Mean whole heart dose was reported in 86 right breast cancer regimens, and the average of these 86 heart doses was 3.7 Gy (IQR 1.2-5.0).

The typical heart doses from left-sided (5.2 Gy) and right-sided (3.7 Gy) radiotherapy were themselves averaged to give 4.4 Gy typical heart dose from 2010s breast cancer radiotherapy assuming approximately equal numbers of women are irradiated for left and right-sided breast cancer.

Calculation of typical 2010s combined lung dose

Whole ipsilateral lung dose was reported for 471 regimens, and the average of these 471 doses was 9.0 Gy (IQR 5.5-12.6). Whole contralateral lung dose was reported for 219 regimens. The average of these 219 doses was 2.4 Gy (IQR 0.4-3.8). Typical ipsilateral and contralateral lung doses were averaged to calculate 5.7 Gy typical combined lung dose for 2010s breast cancer radiotherapy.

Finally, the 104 regimens that reported only total combined lung dose (rather than ipsilateral and contralateral lungs separately) were considered. Coincidentally, in these regimens, the combined lung dose was also 5.7 Gy.

A similar calculation based on publications between 1/1/2010-1/6/2015 i.e. excluding the final 6 months of year 2015, yielded 4.3 Gy typical 2010s heart dose and 5.3 Gy typical 2010s combined lung dose. Hence the values of typical 2010s doses vary slightly according to the time period included.

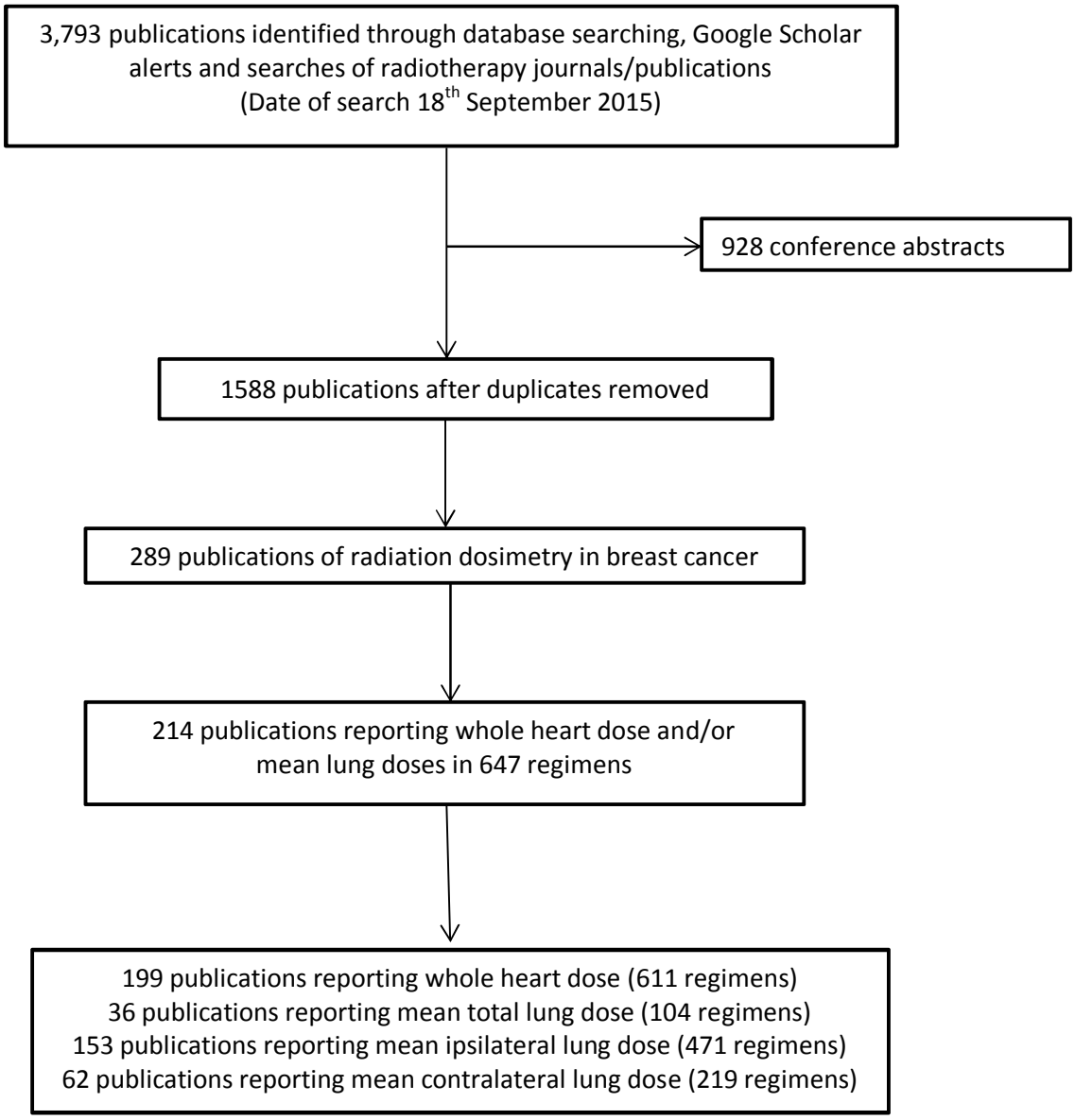
The typical 2010s heart and combined lung doses were rounded to 4 Gy heart dose and 5 Gy whole lung dose and used to estimate the absolute hazards of typical 2010s breast cancer radiotherapy (figure 3).

References

http://www.prisma-statement.org/. Accessed 2.7.15

Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the heart in breast cancer radiotherapy: A systematic review of heart doses published during 2003-2013. Int J Radiat Oncol Biol Phys 2015; **93:** 845-53.

The process of study identification for the review



Reference S1. Studies reporting mean lung or heart doses from breast cancer radiotherapy published 2010-15.

Aaron J, Sasidharan B, Ebenezer S, Thangakunam B, Antonisamy B, Selvamani B. Impact of breathing on post-mastectomy radiotherapy: A dosimetric comparison between intensity-modulated radiotherapy and 3D tangential radiotherapy. J Radiother Pract 2014;14:126-34.

Abo-Madyan Y, Aziz MH, Aly MMOM, et al. Second cancer risk after 3D-CRT, IMRT and VMAT for breast cancer. Radiother Oncol 2014;110:471-6.

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Figure S16. Early Breast Cancer Trialists' Collaborative Group collaborators, listed alphabetically by institution and then name.

AARTM 048/13/2000 Multicentre Study Group, Spain—J A Alberro, B Ballester, P Deulofeu, R Fábregas, M Fraile, J M Gubern, J Janer, A Moral, J L de Pablo, G Peñalva, P Puig, M Ramos, R Rojo, P Santesteban, C Serra, M Solà, L Solarnau, J Solsona, E Veloso, S Vidal.
ACETBC, Tokyo, Japan—O Abe, R Abe, K Enomoto, K Kikuchi, H Koyama, H Masuda, Y Nomura, Y Ohashi, K Sakai, K Sugimachi, M Toi, T Tominaga, J Uchino, M Yoshida.
Addenbrooke's Hospital, Cambridge, UK—J L Haybittle.
Anglo-Celtic Cooperative Oncology Group, UK—C F Leonard.
ARCOSEIN Group, France—G Calais, P Garaud.
ATLAS Trial Collaborative Study Group, Oxford, UK—V Collett, C Davies, A Delmestri, J Sayer.
Auckland Breast Cancer Study Group, New Zealand—V J Harvey, I M Holdaway, R G Kay, B H Mason.
Australian New Zealand Breast Cancer Trials Group, Sydney, Australia—J F Forbes, N Wilcken.
Austrian Breast Cancer Study Group, Vienna, Austria—R Bartsch, P Dubsky, C Fesl, H Fohler, M Gnant, R Greil, R Jakesz, A Lang, G Luschin-Ebengreuth, C Marth, B Mlineritsch, H Samonigg, C F Singer, G G Steger, H Stöger.
Beatson Oncology Centre, Glasgow, UK—P Canney, H M A Yosef.
Belgian Adjuvant Breast Cancer Project, Liège, Belgium—C Focan.
Berlin-Buch Akademie der Wissenschaften, Germany—U Peek.
Birmingham General Hospital, UK—G D Oates, J Powell.
Bordeaux Institut Bergonié, France—M Durand, L Mauriac.
Bordet Institute, Brussels, Belgium—A Di Leo, S Dolci, D Larsimont, J M Nogaret, C Philippson, M J Piccart.
Bradford Royal Infirmary, UK—M B Masood, D Parker, J J Price.
Breast Cancer International Research Group (BCIRG)—M A Lindsay, J Mackey, M Martin.
Breast Cancer Study Group of the Comprehensive Cancer Centre, Limburg, Netherlands—P S G J Hupperets.
British Association of Surgical Oncology BASO II Trialists, London, UK—T Bates, R W Blamey, U Chetty, I O Ellis, E Mallon, D A L Morgan, J Patnick, S Pinder.
British Columbia Cancer Agency, Vancouver, Canada—I Olivotto, J Ragaz.
Cancer and Leukemia Group B, Washington DC, USA—D Berry, G Broadwater, C Cirrincione, H Muss, L Norton, R B Weiss.
Cancer Care Ontario, Canada—H T Abu-Zahra.
Cancer Research Centre of the Russian Academy of Medical Sciences, Moscow, Russia—S M Portnoj.
Cancer Research UK Clinical Trials Unit (CRCTU), NCRI, Birmingham, UK—S Bowden, C Brookes, J Dunn, I Fernando, M Lee, C Poole, D Rea, D Spooner.
Cardiff Trialists Group, UK—P J Barrett-Lee, R E Mansel, I J Monypenny.
Case Western Reserve University, Cleveland, OH, USA—N H Gordon.
Central Oncology Group, Milwaukee, WI, USA—H L Davis.
Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary, University of London, UK—J Cuzick, I Sestak.
Centre Léon-Bérard, Lyon, France—Y Lehingue, P Romestaing.
Centre Paul Lamarque, Montpellier, France—J B Dubois.
Centre Regional François Baclesse, Caen, France—T Delozier, B Griffon, J Mace Lesec'h.
Centre René Huguenin, Paris, St Cloud, France—E Brain, B de La Lande, E Mouret-Fourme.
Centro Oncologico, Trieste, Italy—G Mustacchi.
Charles University in Prague, First Faculty of Medicine, Department of Oncology of the First Faculty of Medicine and General Teaching Hospital, Czech Republic—L Petruzelka, O Pribylova.
Cheltenham General Hospital, UK—J R Owen.
Chemo N0 Trial Group, Germany—N Harbeck, F Jänicke, C Meisner, M Schmitt, C Thomssen.
Chicago University, IL, USA—P Meier.
Chinese Academy of Medical Sciences, Beijing, People's Republic of China (in collaboration with the Oxford CTSU)—Y Shan, Y F Shao, X Wang, D B Zhao (CTSU: Z M Chen, H C Pan).
Christie Hospital and Holt Radium Institute, Manchester, UK—A Howell, R Swindell.

Clinical Trial Service Unit (CTSU), Oxford, UK (ie, members of the CTSU-based EBCTCG Secretariat)—R Bradley, J Braybrooke, J A Burrett, M Clarke, D Cutter, C Davies, D Dodwell, F Duane, V Evans, L Gettins, J Godwin, R Gray, S James, A Kerr, H Liu, E MacKinnon, G Mannu, P McGale, T McHugh, P Morris, H C Pan, R Peto, S Read, C Taylor, Y Wang, Z Wang.
Coimbra Instituto de Oncologia, Portugal—J Albano, C F de Oliveira, H Gervásio, J Gordilho.
Copenhagen Breast Cancer Trials, Copenhagen, Denmark—B Ejlertsen, M-B Jensen, H Johansen, H Mouridsen, T Palshof.
Dana-Farber Cancer Institute, Boston, MA, USA—R S Gelman, J R Harris, D Hayes, C Henderson, C L Shapiro, E Winer.
Danish Breast Cancer Cooperative Group, Copenhagen, Denmark— P Christiansen, B Ejlertsen, M Ewertz, M-B Jensen, S Møller, H T Mouridsen.
Düsseldorf University, Germany—H J Trampisch.
Dutch Working Party for Autologous Bone Marrow Transplant in Solid Tumours, Amsterdam & Groningen, Netherlands—O Dalesio, E G E de Vries, S Rodenhuis, H van Tinteren.
Eastern Cooperative Oncology Group, Boston, MA, USA—R L Comis, N E Davidson, R Gray, N Robert, G Sledge, L J Solin, J A Sparano, D C Tormey, W Wood.
Edinburgh Breast Unit, UK—D Cameron, U Chetty, J M Dixon, P Forrest, W Jack, I Kunkler.
Elim Hospital, Hamburg, Germany—J Rossbach.
Erasmus MC/Daniel den Hoed Cancer Center, Rotterdam, Netherlands— J G M Klijn, A D Treurniet-Donker, W L J van Putten.
European Institute of Oncology, Milan, Italy—N Rotmensz, U Veronesi, G Viale.
European Organization for Research and Treatment of Cancer, Brussels, Belgium—H Bartelink, N Bijker, J Bogaerts, F Cardoso, T Cufer, J P Julien, E Rutgers, C J H van de Velde.
Evanston Hospital, IL, USA—M P Cunningham.
Finnish Breast Cancer Group, Finland—R Huovinen, H Joensuu.
Fondazione Maugeri Pavia, Italy—A Costa.
Fondazione Michelangelo, Milan, Italy—G Bonadonna, L Gianni, P Valagussa.
Fox Chase Cancer Center, Philadelphia, PA, USA—L J Goldstein.
French Adjuvant Study Group (GFEA), Guyancourt, France—J Bonneterre, P Fargeot, P Fumoleau, P Kerbrat, E Luporsi, M Namer.
German Adjuvant Breast Group (GABG), Frankfurt, Germany—W Eiermann, J Hilfrich, W Jonat, M Kaufmann, R Kreienberg, M Schumacher.
German Breast Cancer Study Group (BMFT), Freiburg, Germany—G Bastert, H Rauschecker, R Sauer, W Sauerbrei, A Schauer, M Schumacher.
German Breast Group (GBG), Neu-Isenburg, Germany—J U Blohmer, S D Costa, H Eidtmann, B Gerber, C Jackisch, S Loibl, G von Minckwitz.
Ghent University Hospital, Belgium—A de Schryver, L Vakaet.
GIVIO Interdisciplinary Group for Cancer Care Evaluation, Chieti, Italy—M Belfiglio, A Nicolucci, F Pellegrini, M C Pirozzoli, M Sacco, M Valentini.
Glasgow Victoria Infirmary, UK—C S McArdle, D C Smith, S Stallard.
Groote Schuur Hospital, Cape Town, South Africa—D M Dent, C A Gudgeon, A Hacking, E Murray, E Panieri, ID Werner.
Grupo Español de Investigación en Cáncer de Mama (GEICAM), Spain—E Carrasco, M Martin, M A Segui.
Gruppo Oncologico Clinico Cooperativo del Nord Est, Aviano, Italy—E Galligioni.
Grupo Oncológico Cooperativo del Sur (GOCS), Argentina—B Leone, C T Vallejo, A Zwenger.
Gruppo Oncologico Dell'Italia Meridionale (GOIM), Rome, Italy—M Lopez.
Guadalajara Hospital de 20 Noviembre, Mexico—A Erazo, J Y Medina.
Gunma University, Japan—J Horiguchi, H Takei.
Guy's Hospital, London, UK—I S Fentiman, J L Hayward, R D Rubens, D Skilton.
Heidelberg University I, Germany—H Scheurlen.
Heidelberg University II, Germany—M Kaufmann, H C Sohn.
Helios Klinikum Berlin-Buch, Germany—M Untch.
Hellenic Breast Surgeons Society, Greece—U Dafni, C Markopoulos.
Hellenic Cooperative Oncology Group, Athens, Greece—U Dafni, G Fountzilas.

Hellenic Oncology Research Group, Greece—D Mavroudis.
Helsinki Deaconess Medical Centre, Finland—P Klefstrom.
Helsinki University, Finland—C Blomqvist, T Saarto.
Hospital del Mar, Barcelona, Spain—M Gallen.
Humanitas Cancer Center, Milan, Italy—C Tinterri.
Innsbruck University, Austria—R Margreiter.
Institut Claudius Regaud, Toulouse, France—B de Lafontan, J Mihura, H Roché.
Institut Curie, Paris, France—B Asselain, R J Salmon, J R Vilcoq.
Institut Gustave-Roussy, Paris, France—F André, R Arriagada, S Delaloge, C Hill, S Koscielny,S Michiels, C Rubino.
Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU, NCRI), UK—R A'Hern, J Bliss, P Ellis, L Kilburn, J R Yarnold.
Integraal Kankercentrum, Amsterdam, Netherlands—J Benraadt, M Kooi, A O van de Velde, J A van Dongen, J B Vermorken.
International Breast Cancer Study Group (IBCSG), Bern, Switzerland—M Castiglione, A Coates, M Colleoni, J Collins, J Forbes, R D Gelber, A Goldhirsch, J Lindtner, K N Price, M M Regan, C M Rudenstam, H J Senn, B Thuerlimann.
International Collaborative Cancer Group, Charing Cross Hospital, London, UK—J M Bliss, C E D Chilvers, R C Coombes, E Hall, M Marty.
International Drug Development Institute, Louvain-la-Neuve, Belgium—M Buyse.
International TABLE Study Group, Berlin, Germany—K Possinger, P Schmid, M Untch, D Wallwiener.
IRCCS AOU San Martino – IST Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy–G Canavese, B Dozin.
ISD Cancer Clinical Trials Team (incorporating the former Scottish Cancer Therapy Network), Edinburgh, UK—L Foster, W D George, H J Stewart, P Stroner.
Israel NSABC, Tel Aviv, Israel—R Borovik, H Hayat, M J Inbar, T Peretz, E Robinson.
Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy—P Bruzzi, L Del Mastro, P Pronzato, M R Sertoli, M Venturini.
Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy—T Camerini, F Formelli, G Martelli, M G Di Mauro, P Valagussa.
Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, Italy—F Perrone.
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy—D Amadori.
Italian Cooperative Chemo-Radio-Surgical Group, Bologna, Italy—A Martoni, F Pannuti.
Italian Oncology Group for Clinical Research (GOIRC), Parma, Italy— R Camisa, A Musolino, R Passalacqua.
Japan Clinical Oncology Group–Breast Cancer Study Group, Matsuyama, Japan—K Aogi, S Takashima.
Japanese Foundation for Multidisciplinary Treatment of Cancer, Tokyo, Japan—O Abe, T Ikeda, K Inokuchi, K Kikuchi, K Sawa.
Kawasaki Medical School, Japan—H Sonoo.
Klinikum Bayreuth, Germany—M Sadoon, A H Tulusan.
Kobe Breast Cancer Oncology Group, Japan—N Kohno, M Miyashita, S Takao.
Korean Cancer Study Group (KCSG), Seoul, South Korea—J.-H Ahn, K H Jung.
Krakow Institute of Oncology, Poland—S Korzeniowski, J Skolyszewski.
Kumamoto University Group, Japan—M Ogawa, J Yamashita.
Leiden University Medical Center, Netherlands—E Bastiaannet, G J Liefers, C J H van de Velde.
Leuven Akademisch Ziekenhuis, Gasthuisberg, Belgium—R Christiaens, P Neven, R Paridaens, W Van den Bogaert.
Ludwig-Maximilians University, Munich, Germany—S Braun.
Marseille Laboratoire de Cancérologie Biologique APM, France—P Martin, S Romain.
Medical University Vienna – General Hospital - Department of Obstetrics and Gynaecology and Department of Medicine I, Vienna, Austria—M Janauer, M Seifert, P Sevelda, C C Zielinski.
Memorial Sloan-Kettering Cancer Center, New York, NY, USA—T Hakes, C A Hudis, L Norton, R Wittes.
Metaxas Memorial Cancer Hospital, Athens, Greece—G Giokas, D Kondylis, B Lissaios.
Mexican National Medical Center, Mexico City, Mexico—R de la Huerta, M G Sainz.
National Cancer Center, Goyang, South Korea—J Ro.
National Cancer Institute, Bethesda, MD, USA—R Altemus, K Camphausen, K Cowan, D Danforth, A Lichter, M Lippman, J O'Shaughnessy, L J Pierce, S Steinberg, D Venzon, J A Zujewski.

National Cancer Institute of Bari, Italy—C D'Amico, M Lioce, A Paradiso.
NCIC Clinical Trials Group, Kingston, Ontario, Canada—J-A W Chapman, B E Chen, K Gelmon, P E Goss, M N Levine, R Meyer, W Parulekar, J L Pater, K I Pritchard, L E Shepherd, D Tu, T Whelan.
National Kyushu Cancer Center, Japan—Y Nomura, S Ohno.
National Surgical Adjuvant Breast and Bowel Project (NSABP), Pittsburgh, PA, USA—S Anderson, G Bass, A Brown (deceased), J Bryant (deceased), J Costantino, J Dignam, B Fisher, C Geyer, E P Mamounas, S Paik, C Redmond, S Swain, L Wickerham, N Wolmark.
National Surgical Adjuvant Study Group (N-SAS-BC), Japan—T Aihara, Y Hozumi, Y Nomura.
Nolvadex Adjuvant Trial Organisation, London, UK—M Baum, I M Jackson (deceased), M K Palmer.
North Central Cancer Treatment Group, Mayo Clinic, Rochester, MN, USA—E Perez, J N Ingle, V J Suman.
North Sweden Breast Cancer Group, Umeå, Sweden—N O Bengtsson, S Emdin, H Jonsson.
North-West Oncology Group (GONO), Italy—L Del Mastro, M Venturini.
North-Western British Surgeons, Manchester, UK—J P Lythgoe, R Swindell.
Northwick Park Hospital, London, UK—M Kissin.
Norwegian Breast Cancer Group, Oslo, Norway—B Erikstein, E Hannisdal, A B Jacobsen, K V Reinertsen, J E Varhaug.
Norwegian Radium Hospital, Oslo, Norway—B Erikstein, S Gundersen, M Hauer-Jensen, H Høst, A B Jacobsen, R Nissen-Meyer.
Nottingham City Hospital, UK—R W Blamey, A K Mitchell, D A L Morgan, J F R Robertson.
Oita Prefectural Hospital, Japan—H Ueo.
Oncofrance, Paris, France—M Di Palma, G Mathé (deceased), J L Misset.
Ontario Clinical Oncology Group, Hamilton, Canada—M Levine, K I Pritchard, T Whelan.
Osaka City University, Japan—K Morimoto.
Osaka National Hospital, Japan—K Sawa, Y Takatsuka.
Oxford Radcliffe Hospitals NHS Trust, Churchill Hospital, Oxford, UK—E Crossley, A Harris, D Talbot, M Taylor.
Parma Hospital, Italy—G Cocconi, B di Blasio.
Petrov Research Institute of Oncology, St Petersburg, Russia—V Ivanov, R Paltuev, V Semiglazov.
Piedmont Oncology Association, Winston-Salem, NC, USA—J Brockschmidt, M R Cooper.
Pretoria University, South Africa—C I Falkson.
ProBONE study group, Marburg, Germany—P Hadji.
Royal Marsden NHS Trust, London and Sutton, UK—R A'Hern, M Dowsett, A Makris, M Parton, K Pennert, T J Powles, I E Smith, J R Yarnold.
St George's Hospital, London, UK—J C Gazet.
St George Hospital, Sydney, Australia—L Browne, P Graham.
St Luke's Hospital, Dublin, Ireland—N Corcoran.
SABRE trial group (international)—G Clack, C Van Poznak.
Sardinia Oncology Hospital A Businico, Cagliari, Sardinia—N Deshpande, L di Martino.
SASIB International Trialists, Cape Town, South Africa—P Douglas, A Hacking, H Høst, A Lindtner, G Notter.
Saskatchewan Cancer Foundation, Regina, Canada—A J S Bryant, G H Ewing, L A Firth, J L Krushen-Kosloski.
Scandinavian Adjuvant Chemotherapy Study Group, Oslo, Norway—R Nissen-Meyer.
South Sweden Breast Cancer Group, Lund, Sweden—H Anderson, F Killander, P Malmström, L Rydén.
South-East Sweden Breast Cancer Group, Linköping, Sweden—L-G Arnesson, J Carstensen, M Dufmats, H Fohlin, B Nordenskjöld, M Söderberg.
South-Eastern Cancer Study Group and Alabama Breast Cancer Project, Birmingham, AL, USA—J T Carpenter.
Southampton Oncology Centre, UK—N Murray, G T Royle, P D Simmonds.
Southwest Oncology Group, San Antonio, TX, USA—K Albain, W Barlow, J Crowley, D Hayes, J Gralow, G Hortobagyi, R Livingston, S Martino, C K Osborne, P M Ravdin.
Stockholm Breast Cancer Study Group, Sweden—J Adolfsson, J Bergh, T Bondesson, F Celebioglu, K Dahlberg, T Fornander, I Fredriksson, J Frisell, E Göransson, M Iiristo, U Johansson, E Lenner, L Löfgren, P Nikolaidis, L Perbeck, S Rotstein, K Sandelin, L Skoog, G Svane, E af Trampe, C Wadström.
SUCCESS-Study Group, University of Düsseldorf, Germany—W Janni.
Swiss Group for Clinical Cancer Research (SAKK), Bern, and OSAKO, St Gallen, Switzerland—M Castiglione, A Goldhirsch, R Maibach, H J Senn, B Thürlimann.

Tamoxifen Exemestrane Adjuvant Multinational (TEAM) trial— E Bastiaannet, P Hadji, Y Hozumi, D Rea, C J H van de Velde.
Tampere University Hospital, Finland— M Hakama, K Holli, J Isola, K Rouhento, R Saaristo.
Tel Aviv Sourasky Medical Center, Israel—T Safra.
Tel Aviv University, Israel—H Brenner, A Hercbergs.
Tokyo Cancer Institute Hospital, Japan—M Yoshimoto.
Toronto-Edmonton Breast Cancer Study Group, Canada—A H G Paterson, K I Pritchard.
Toronto Princess Margaret Hospital, Canada—A Fyles, J W Meakin, T Panzarella, K I Pritchard.
Tunis Institut Salah Azaiz, Tunisia—J Bahi.
UK Multicentre Cancer Chemotherapy Study Group, London, UK—M Reid, M Spittle.
UK/ANZ DCIS Trial—H Bishop, N J Bundred, J Cuzick, I O Ellis, I S Fentiman, J F Forbes, S Forsyth, W D George, S E Pinder, I Sestak.
UK/Asia Collaborative Breast Cancer Group, London, UK—G P Deutsch, R Gray, D L W Kwong, V R Pai, R Peto, F Senanayake.
Unicancer Breast Group— A L Martin, H Roché.
University and Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy on behalf of GROCTA trialists—F Boccardo, A Rubagotti.
University College London, UK—M Baum, S Forsyth, A Hackshaw, J Houghton, J Ledermann, K Monson, JS Tobias.
University Federico II, Naples, Italy—C Carlomagno, M De Laurentiis, S De Placido.
University of Edinburgh, UK—L Williams.
University of Leeds, UK—R Bell, D Cameron, R E Coleman, D Dodwell, S Hinsley, H C Marshall.
University of Michigan, USA—D Hayes, L J Pierce.
University of Saarland, Germany—E Solomayer, T Fehm.
University of Sheffield, UK—R E Coleman, J M Horsman, J Lester, M C Winter.
University of Texas MD Anderson Cancer Center, Houston, TX, USA—A U Buzdar, L Hsu.
University of Wisconsin, USA—R R Love.
Uppsala-Örebro Breast Cancer Study Group, Sweden—J Ahlgren, H Garmo, L Holmberg, G Liljegren, H Lindman, F Wärnberg.
U.S. Oncology, Houston, USA—L Asmar, S E Jones.
Washington University, St Louis, Missouri, USA—R Aft.
West German Study Group (WSG), Germany—O Gluz, N Harbeck, C Liedtke, U Nitz.
West of Scotland Breast Trial Group, Glasgow, UK—A Litton.
West Sweden Breast Cancer Study Group, Gothenburg, Sweden—A Wallgren, P Karlsson, B K Linderholm.
Western Cancer Study Group, Torrance, CA, USA—R T Chlebowski.
Würzburg University, Germany—H Caffier.
Z-FAST, ZO-FAST & E-ZO-FAST study groups (international)—A M Brufsky, R E Coleman, H A Llombart, on behalf of Novartis Pharmaceuticals.

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MAIN TEXT FIGURES AND TABLES to

Estimating the risks of breast cancer radiotherapy: Evidence from modern radiation doses to the lungs and heart and from previous randomised trials

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Table 1: Data availability from trials of radiotherapy vs not that began by the year 2000*

Trial characteristics				Woman-years (thousands) without recurrence, by years since entry			Deaths	
Surgery	No. of trials	Women		<10	10-19	20+	Without recurrence	Any cause
		Number	Median (IQR) randomisaton year					
Mastectomy	36	16,156	1975 (1972-1983)	96	42	13	2921	11,201
BCS	18	11,655	1992 (1987-1997)	77	18	1	1270	3260
Various†	17	9066	1976 (1972-1983)	59	29	10	1666	5512
BCS for DCIS	4	3904	1992 (1990-1995)	25	5	0	207	372
All trials	**75**	**40,781**	**1983 (1974-1989)**	**257**	**94**	**24**	**6064**	**20,345**

BCS = breast conserving surgery, DCIS = ductal carcinoma-in-situ.

* Individual trial details are in Table S3. For balance, unirradiated controls in six 3-arm trials are counted twice, and four of these trials contribute to two categories of surgery. Datasets were not available from 11 trials which included about 2000 women.

† In some of these trials the control group had more surgery than the radiotherapy group.

Table 2: Effect of allocation to radiotherapy (RT) on incidence of second cancers and on mortality from causes other than breast cancer

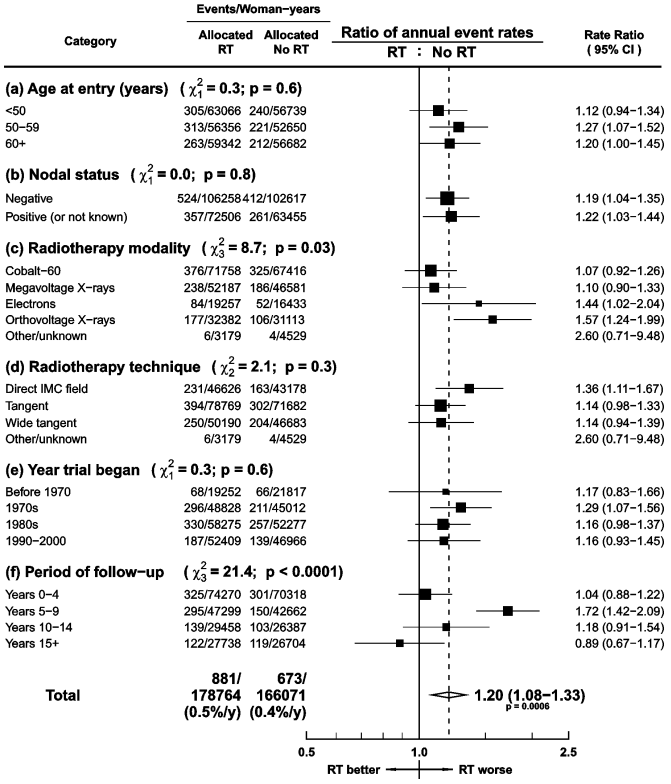
	Number of first events or deaths (total woman-years)				
	RT (194957)	No RT (180250)	Adjusted excess* (95% CI)	Rate ratio (95% CI)	P Value
Second cancer incidence of specified site without prior breast cancer recurrence					
Contralateral breast	881	673	130 (56-204)	1.20 (1.08—1.33)	0.0006
Leukaemia	43	23	17 (2-33)	1.71 (1.05—2.79)	0.03
Lung, years 0-9	71	60	5 (-17-27)	1.08 (0.76—1.53)	0.66
Lung, years 10+	94	40	47 (25-69)	2.10 (1.48—2.98)	<0.0001
Pleura	3	0	2 (-1-5)	-	0.18
Oesophagus	23	10	13 (3-24)	2.42 (1.19—4.92)	0.01
Pancreas	42	25	14 (0-29)	1.64 (0.98—2.76)	0.06
Stomach	55	63	-12 (-32-8)	0.80 (0.55—1.17)	0.25
Large intestine	164	136	19 (-14-51)	1.15 (0.91—1.45)	0.26
Ovary	68	68	-1 (-22-21)	0.99 (0.70—1.41)	0.95
Endometrium	109	83	20 (-6-47)	1.26 (0.94—1.69)	0.12
Cervix	31	27	2 (-13-16)	1.06 (0.62—1.83)	0.83
Melanoma	32	25	7 (-8-21)	1.28 (0.75—2.19)	0.36
Soft tissue	23	17	6 (-6-17)	1.36 (0.71—2.59)	0.35
Lymphoma	45	41	4 (-14-21)	1.09 (0.71—1.70)	0.69
Other specified site	171	143	5 (-7-58)	1.20 (0.95—1.51)	0.13
All sites except breast	**974**	**761**	**168 (90-246)**	**1.23 (1.12—1.36)**	**<0.0001**
Death without breast cancer recurrence					
Ischaemic heart disease	424	327	90 (39-140)	1.31 (1.13—1.53)	0.0005
Heart failure	63	33	28 (10-46)	1.94 (1.27—2.98)	0.002
Heart valve disease	31	15	14 (1-26)	1.97 (1.07—3.67)	0.03
Other heart disease	187	173	11 (-14-36)	1.08 (0.86—1.35)	0.52
Subtotal: All cardiac	*705*	*548*	*143 (78-208)*	*1.30 (1.15—1.46)*	*<0.0001*
Cancer of specified site	475	375	67 (12-121)	1.19 (1.03—1.37)	0.02
Other specified cause	638	629	6 (-78-91)	1.01 (0.90—1.14)	0.83
Subtotal: Specified cause	*1818*	*1552*	*216 (111-322)*	*1.16 (1.08—1.25)*	*<0.0001*
Unspecified cause	1413	1281	153 (58-247)	1.14 (1.05—1.24)	0.002
All causes of death except breast cancer	**3231**	**2833**	**369 (228-510)**	**1.15 (1.09—1.22)**	**<0.0001**

* The adjusted excess number of events (or deaths) in the RT group is calculated as twice the logrank Observed minus Expected (see Methods S1 for details) and allows for RT delaying recurrence.

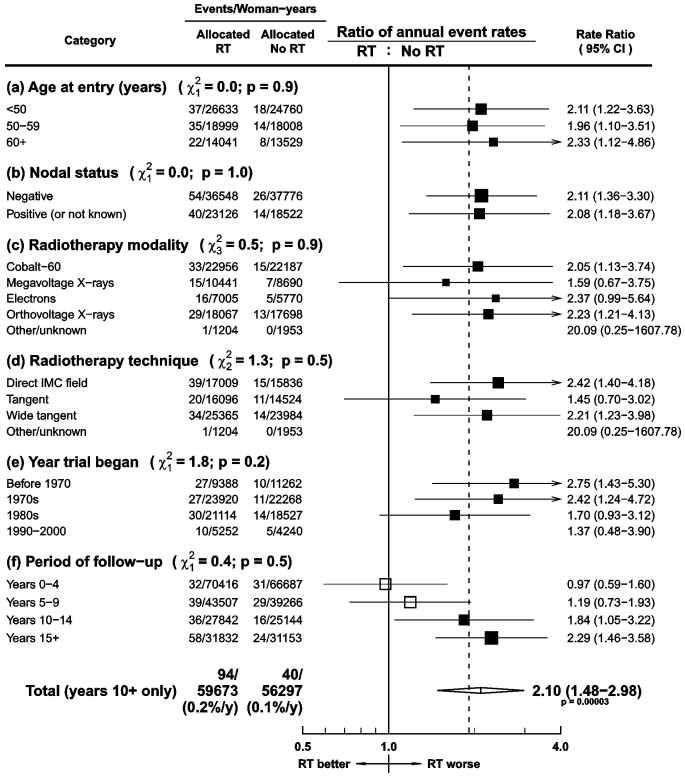
Cancer incidence: Excludes non-melanoma skin cancer. Other specified sites include uterus, part unspecified.

Figure 1: Effect of allocation to radiotherapy (RT) on contralateral breast cancer and on lung cancer incidence (years 10+)

Contralateral breast cancer incidence (65 trials)



Lung cancer incidence during years 10+ (30 trials)



Areas of squares are proportional to amounts of information, open boxes do not contribute to test for trend.
IMC=internal mammary chain

Figure 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, 4-8, and 8+ Gy, with mean doses 2.1, 5.8, and 12.6 Gy.

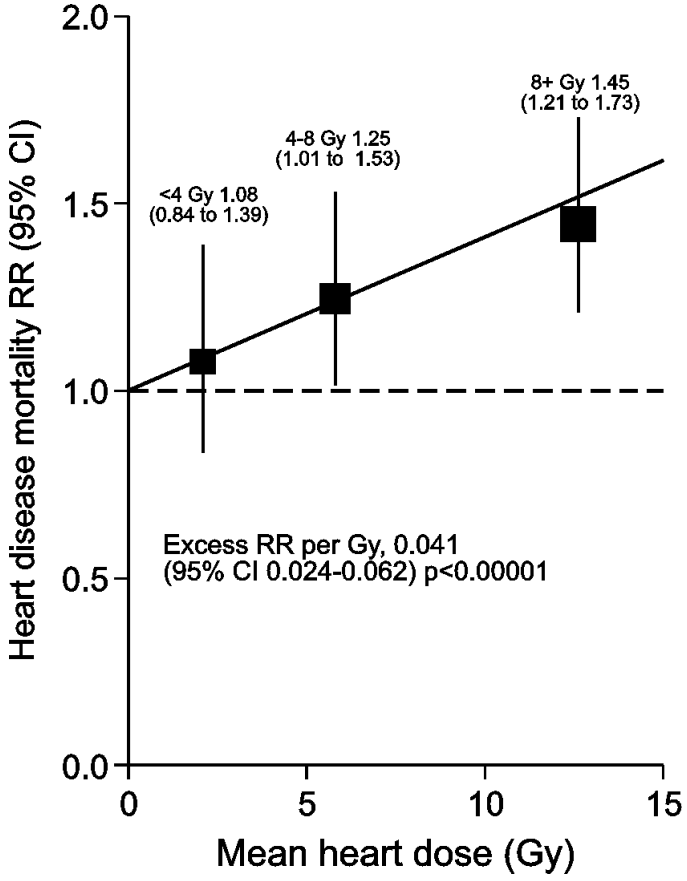


Figure 3: Estimated effects among 50-year-old smokers and non-smokers of typical 2010s radiotherapy regimens on mortality from (a) lung cancer and (b) ischaemic heart disease (IHD)

Epidemiological 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 (see Methods S1 for methodology).