

# **Cardiac Structure Injury after Breast Cancer Radiotherapy:**

## **Cross-sectional Study with Individual Patient Data**

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## **Abstract**

**Purpose** Incidental cardiac irradiation can cause cardiac injury, but little is known about the effect of radiation on specific cardiac segments.

**Methods** For 456 women who received breast cancer radiotherapy during 1958-2001 and later experienced a major coronary event, information was obtained on their radiotherapy and their cardiac injury. For 414 women, all with documented location of left-ventricular (LV) injury, doses to five LV segments were estimated. For 133 women, all with documented location of coronary artery disease with  $\geq 70\%$  stenosis, doses to six coronary artery segments were estimated. For each segment, numbers of women with left-sided and right-sided breast cancer were compared.

**Results** For women with LV injury, 243 had left-sided and 171 right-sided breast cancer (left-versus-right ratio: 1.42, 95%CI 1.17-1.73) reflecting the higher typical LV radiation doses in left-sided cancer (average left-sided: 8.3 Gy, right-sided: 0.6 Gy, left-minus-right dose difference: 7.7 Gy). For individual LV segments, left-versus-right ratios were: inferior 0.94 (95%CI 0.70-1.25), lateral 1.42 (1.04-1.95), septal 2.09 (1.37-3.19), anterior 1.85 (1.39-2.46), apex 4.64 (2.42-8.90), with corresponding left-minus-right dose differences of 2.7, 4.9, 7.2, 10.4 and 21.6 Gy ( $p_{\text{trend}} < 0.00001$ ). For women with coronary artery disease, left-versus-right ratios for individual coronary artery segments were: right coronary artery (RCA) proximal 0.48 (0.26-0.91), RCA mid/distal 1.69 (0.85-3.36), circumflex proximal 1.46 (0.72-2.96), circumflex distal 1.11 (0.45-2.73), left anterior descending (LAD) proximal 1.89 (1.07-3.34), LAD mid/distal 2.33 (1.19-4.59), with corresponding left-minus-right dose differences of -5.0, -2.5, 1.6, 3.5, 9.5, and 38.8 Gy ( $p_{\text{trend}}: 0.002$ ).

**Conclusion** For individual left ventricle and coronary artery segments, higher radiation doses were strongly associated with more frequent injury, suggesting they are all sensitive to radiation, and doses to all segments should be minimised.

## Introduction

Radiotherapy with curative intent is given to many patients with cancer. In breast cancer, it reduces the risks of recurrence and death,<sup>1,2</sup> but incidental cardiac irradiation may increase the risk of heart disease.<sup>3–5</sup> Thoracic radiotherapy can also increase heart disease risk in Hodgkin lymphoma, childhood cancer, oesophageal cancer, and lung cancer.<sup>6,7</sup> Ischemic heart disease (IHD) is the commonest type affected, and radiation-related risk increases approximately linearly with mean whole heart radiation dose.<sup>6,8,9</sup>

Radiation-related IHD may be caused by microvascular myocardial disease or macrovascular coronary artery disease.<sup>7</sup> Doses from radiotherapy to individual myocardial or coronary artery segments differ substantially depending on regimen, and regimens differ by tumour type, stage and location and, for breast and lung cancer, laterality.<sup>10,11</sup> Considerable resources are being invested in reducing cardiac exposure from radiotherapy.<sup>12,13</sup> At present, however, little is known about the long-term effects of irradiating specific segments of the left ventricle (LV) or coronary arteries. Such knowledge may help guide the adoption of cardiac-sparing techniques, as well as helping oncologists to identify the optimal radiotherapy plan for each individual patient.

Several studies have provided insight into the risk of radiation-related heart disease following breast cancer radiotherapy by comparing the numbers of women with left-sided and right-sided breast cancer and calculating the likely difference in cardiac dose between the two groups.<sup>7,8</sup> Here we extend this technique by considering women irradiated for breast cancer who subsequently developed IHD and for whom

the location (segment) of cardiac injury and the radiotherapy regimen, including cancer laterality, were documented. Any differences between women irradiated for left-sided compared with right-sided breast cancer in the distribution of cardiac injuries across the different cardiac segments is likely to reflect differences in the spatial distribution of radiation received by different segments during left-sided and right-sided radiotherapy.

In this study, for each cardiac segment, we calculated the ratio of the number of women with injury to that segment following left-sided radiotherapy to the number of women with injury to that segment following right-sided radiotherapy. We related these ratios to differences in the typical doses delivered to the various segments from left-sided and right-sided radiotherapy.

## **Methods**

All women who received adjuvant breast cancer radiotherapy in Stockholm during 1958-2001 or Denmark during 1977-2000 and who subsequently had a major coronary event (defined as myocardial infarction (International Classification of Diseases, 10th Revision [ICD-10] codes I21–I24), coronary revascularization (Nordic Medico-Statistical Committee Classification of Surgical Procedures, version 1.9, code FN), or death from IHD (hospital or community) (ICD-10 codes I20–I25) were identified from Swedish national patient and cause of death registers and the Danish Breast Cancer Cooperative Group, patient discharge, and cause of death registers.<sup>8</sup> Each woman's radiotherapy regimen and medical history before breast cancer diagnosis were abstracted from her hospital oncology record. Women without

histopathological confirmation of cancer, with bilateral or metastatic disease, previous cancer (except non-melanoma skin cancer), previous thoracic radiotherapy, or whose breast cancer recurred before their major coronary event, were excluded. A total of 963 eligible women were identified. The study was approved by the Danish Data Protection Agency and by the ethics review board of the Karolinska Institutet in Stockholm.

#### *Location and type of cardiac injury*

Hospital cardiology notes were sought for all 963 women. Information on the location, nature, and extent of any LV myocardial injury and on any disease of the left anterior descending (LAD), right, and circumflex coronary arteries was abstracted by four research nurses. Two cardiologists and an oncologist (KR,BG,CC) who were blinded to the cancer laterality used this information to code site of injury. Injury location included five LV segments (anterior, inferior, apex, lateral, septal) (appendix p2) and two segments (proximal, mid/distal or distal) of each of the LAD, right and circumflex coronary arteries.<sup>14</sup> LV injury was defined as evidence of: myocardial infarction on electrocardiogram (ECG), permanent perfusion defects on multiple-gated acquisition (MUGA) or myocardial perfusion scan, regional wall-motion abnormalities on echocardiogram, or LV infarction on autopsy record. Coronary artery disease was defined as  $\geq 70\%$  coronary artery stenosis at angiogram or autopsy. Coronary artery disease with  $< 70\%$  stenosis was excluded as it is often subclinical, so would be under-reported. Information on other locations (e.g. right ventricle) was rarely reported in cardiology notes so was not included.

### *Radiation dosimetry*

Radiation doses were estimated for five LV segments and two segments of the LAD, right and circumflex coronary arteries (fig. 1, fig. 2, appendix p3-6).<sup>14</sup> First, each woman's radiotherapy chart was used to categorise her according to regimen. Second, a "typical CT-scan" was selected. Third, all regimens were reconstructed on the "typical CT-scan" to derive regimen-specific doses for each segment. Fourth, each woman was allocated segment doses according to regimen and total dose. Fifth, dosimetry uncertainties were assessed.

### *Statistical methods*

Radiation dose estimates for individual cardiac segments were available only for women with recorded cardiac injury, and not for otherwise comparable women in the population without a major coronary event. Therefore it was not possible to assess dose-response relationships in terms of the percentage increase per Gy in segment injury rate.

Separate analyses were conducted for LV and coronary arteries. The ratio of the number of women receiving left-sided radiotherapy to the number receiving right-sided radiotherapy was calculated ("left-versus-right ratio"). Tests for heterogeneity in the left-right ratio with various characteristics were conducted using logistic regression.

For each injured LV or coronary artery segment, the typical dose to that segment was calculated, based on radiotherapy regimen, including cancer laterality. The average of the typical doses was then calculated separately for left-sided and right-



sided cancer, and the difference between these average typical doses derived (“left-minus-right dose difference”). The segments were then ranked according to left-minus-right dose differences. A test for trend in the left-versus-right ratios was conducted using logistic regression with rank as the independent variable (appendix p7-10). Calculations were performed with Stata statistical software version 13.0 (StataCorp LP, College Station, TX).

## **Results**

Location of cardiac injury was identified for 456 women and these were included in the study. The other 507 eligible women were not included because their cardiology record was unavailable (250/963), their injury location was not documented (243/963), or their regimen was identical in left-sided and right-sided breast cancer (14/963) (appendix p11).

### *LV injury*

Information on location of LV injury was obtained for 712 LV segments in 414 women. The case-defining event was myocardial infarction in 91% (376/414) of women, coronary artery disease in 7% (29/414), and death certificate information in 2% (9/414) (table 1, left panel). For 57% (234/414), available information included at least one of the following: echocardiogram, MUGA or myocardial perfusion scan, or autopsy. For the remaining 43% (180/414), information on LV injury location was available only from ECGs.

Radiotherapy was for left-sided cancer in 243 women and right-sided in 171, giving a left-versus-right ratio of 1.42 (95% confidence interval (CI) 1.17-1.73), resulting from the larger LV radiation doses in left-sided cancer (average of typical LV doses in women with LV injury: left-sided 8.3 Gy, right-sided 0.6 Gy; left-minus-right dose difference: 7.7 Gy). The left-versus-right ratio did not vary significantly according to initial information on case-defining event, type of information documenting the injury location, or presence of cardiac risk factors at time of cancer diagnosis ( $p_{\text{heterogeneity}} > 0.10$  for all three factors).

Average whole heart doses were 6.9 Gy in left-sided and 3.2 Gy in right-sided radiotherapy. Exposure of the heart was non-uniform for all regimens, with substantial variation in doses received by different cardiac segments (fig. 2). For left-breast cancer, the LV apex received the highest doses for most regimens. For right-breast cancer, the entire LV was outside the fields for most regimens.

Ninety women had injury to the inferior LV segment after left-sided radiotherapy versus 96 after right-sided radiotherapy, giving a left-versus-right ratio of 0.94 (95% CI 0.70-1.25) (fig. 3 panel c). The average typical inferior segment doses were 3.7 Gy in left-sided radiotherapy and 1.0 in right-sided radiotherapy, giving a left-minus-right difference of 2.7 Gy. For other segments the left-versus-right ratios were: lateral 1.42 (1.04-1.95), septal 2.09 (1.37-3.19), anterior 1.85 (1.39-2.46), and apex 4.64 (2.42-8.90), following left-minus-right differences in segment dose of 4.9, 7.2, 10.4, and 21.6 Gy respectively ( $p_{\text{trend}}$  across all segments:  $< 0.00001$ ).

Twenty radiotherapy techniques were used (appendix p5). For the two commonest (tangential and anterior electron/orthovoltage), the left-versus-right ratios of women with injury to individual LV segments increased with increasing left-minus-right segment dose difference in each ( $p_{\text{trend}}$ : tangential 0.005, anterior electron/orthovoltage 0.004; fig. 3, panels a&b, appendix p15).

The left-versus-right ratio of injury increased with the left-minus-right difference in typical dose both for the 99 women irradiated after breast-conserving surgery ( $p_{\text{trend}}$ : 0.05, fig. 4 panel a) and for the 315 women irradiated after mastectomy ( $p_{\text{trend}}$ : <0.00001) (fig. 4 panel c). Ninety of the 99 women given breast-conserving surgery received tangential radiotherapy and in them the left-versus-right ratio of injury still tended to increase with the left-minus-right difference in typical dose ( $p_{\text{trend}}$ : 0.06) (fig. 4 panel b).

### *Coronary artery disease*

Information on location of coronary artery stenosis was obtained for 221 segments in 133 women. The initial case-defining event was myocardial infarction in 51% (68/133) of the women, coronary artery disease in 43% (57/133), and death certificate information in 6% (8/133) (table 1, right panel). Coronary angiography was available for all 133 women, and for 19 an autopsy report was also available. Eighty women were irradiated for left-sided and 53 for right-sided cancer (left-versus-right ratio: 1.51, 95% CI 1.07-2.14), with typical doses to the main coronary arteries combined of 8.0 Gy and 0.6 Gy respectively. As with LV injury, the left-versus-right ratio did not vary significantly according to the initial case-defining event information,

type of information documenting location of injury, or presence of cardiac risk factors at breast cancer diagnosis ( $p_{\text{heterogeneity}} \geq 0.10$  for all three factors).

Average whole heart doses were 7.1 Gy in left-sided and 3.1 in right-sided radiotherapy. For left-sided radiotherapy, part of the LAD coronary artery was included in the fields for most regimens, whereas part of the right coronary artery was usually irradiated in right-sided radiotherapy (fig 2). Left-versus-right ratios of women with disease in any of the six individual coronary artery segments were: proximal right: 0.48 (95% CI 0.26-0.91), mid/distal right: 1.69 (0.85-3.36), proximal circumflex: 1.46 (0.72-2.96), distal circumflex: 1.11 (0.45-2.73), proximal LAD: 1.89 (1.07-3.34), and mid/distal LAD: 2.33 (1.19-4.59) following left-minus-right dose differences of -5.0, -2.5, 1.6, 3.5, 9.5, and 38.8 Gy respectively ( $p_{\text{trend}}: 0.002$ , fig. 5 panel d).

When women given radiotherapy after breast-conserving surgery and mastectomy were considered separately, the left-versus-right ratio of segment injury increased with left-minus-right segment dose difference for both ( $p_{\text{trend}}$  breast-conserving surgery: 0.02, mastectomy: 0.05; fig. 5 panels a&c). Notably, for radiotherapy after mastectomy, typical doses to the right coronary artery proximal segment were higher for right-sided than left-sided radiotherapy (left-sided 10.8 Gy, right-sided 15.1 Gy, left-minus-right dose difference -4.3 Gy) and more women with right-sided than left-sided breast cancer had disease of this segment (left-right-ratio: 0.42, 95% CI 0.20-0.87). Results were for whole coronary arteries were similar (appendix p16).

## Discussion

We have extended the commonly-used technique of comparing the numbers of women with heart disease following radiotherapy for left-sided and right-sided breast cancer to provide insight into the effect of radiotherapy on individual segments of the LV and coronary arteries. We have shown that, for segments where there was little difference in the typical dose received from radiotherapy for left-sided and right-sided breast cancer, the left-versus-right ratios of the numbers of women with injury were close to one. However, as the differences in typical segment dose between left-sided and right-sided cancer increased, so did the left-versus-right ratios of the numbers of women with injury to the segment concerned. Most increases were statistically significant when the left-minus-right difference in typical dose was more than ~4 Gy. Notably, where the typical dose from *right-sided* radiotherapy was more than 4 Gy higher than from left-sided radiotherapy, the left-versus-right ratio of the number of women with injury was significantly *lower* than one. Radiation-related increases in injury were seen throughout the cardiac structures studied, including the lateral, septal, anterior, and apex LV segments, the proximal right coronary artery segment, and the proximal and mid/distal LAD segments. These findings strongly suggest a close and direct relation between radiation exposure and injury to different segments of the LV and coronary arteries.

The 963 women eligible for this study formed the cases in a population-based case-control study. Any differences between the 456 women included in this study and the remaining 507 are unlikely to have biased our results (appendix p11,12). For the women studied, it is unlikely that breast cancer laterality affected the decision to give radiotherapy or the regimen used: in the population from which the women were

drawn, the ratio of the number of women irradiated for left-sided versus the number irradiated for right-sided cancer was 1.1 (left-breast cancer incidence is slightly higher than right-breast cancer) and the characteristics of the women irradiated for left-sided and right-sided cancer were virtually identical, as was their subsequent mortality from all causes other than heart disease.<sup>5</sup> Hence, it is likely that the increases reported are causally-related to radiation.

A limitation of our study was that individual CT-information was unavailable because the women were irradiated before the era of 3-dimensional CT-radiotherapy planning. It was, therefore, necessary to estimate cardiac doses retrospectively using a “typical CT-scan”. Reassuringly, our cardiac dose estimates are similar to other estimates from these regimens.<sup>15,16</sup> Furthermore we showed that dosimetric uncertainties had little effect on the use we made of our segment dose estimates (appendix p3-6).

A second limitation is that for most women with LV injury, we did not have information on possible disease of the coronary artery supplying the segment concerned. Nevertheless, for 91 women with information on both coronary artery disease and LV injury, LV injury tended to occur in segments supplied by the diseased coronary arteries (appendix p17). This may be due to radiation-related coronary artery disease causing LV ischemia downstream. Alternatively, it may be due to proximity of the coronary arteries to the LV segments they supply, resulting in similar radiation doses being received by both. Doses to many LV and coronary artery segments were highly correlated (appendix p18,19). Hence, in our study we

could not tell whether radiation-related LV injury was caused directly by LV irradiation or indirectly by radiation-related coronary artery disease.

Myocardial perfusion defects (ischemic areas of the LV) after breast cancer radiotherapy have been demonstrated in studies involving around 600 women in total. In some studies, women had cardiac imaging before, then months or years after, left-sided radiotherapy and each woman's pre- and post-radiotherapy images compared. In other studies, cardiac imaging was performed between 5 and 19 years after radiotherapy, and images of women given left-sided, right-sided, or no radiotherapy compared.<sup>17,18</sup> The results of these studies are consistent with our study, although the clinical implications of the abnormalities are unknown. The myocardial perfusion studies did not provide segment doses, but several of them showed that the location of LV perfusion defects was determined by the borders of radiotherapy fields, rather than the distribution of major coronary vessels. This suggests defects were caused by damage to the myocardial microvasculature rather than coronary artery damage.<sup>19</sup> In two echocardiography studies, including 70 women with tangential radiotherapy, LV segment doses were related to subsequent segment function before, and a few weeks after, radiotherapy.<sup>20,21</sup> The LV apex received the highest doses from left-tangential radiotherapy, and had poorer function after radiotherapy than other segments. Function was significantly reduced in LV segments that received >3 Gy.

Disease of the main coronary arteries has been demonstrated in three studies of patients referred for angiography some years after radiotherapy.<sup>22-24</sup> The studies, based on a total of 149 irradiated patients, found that coronary stenoses occurred

preferentially in arterial segments likely to have received high radiation doses and are consistent with our findings.

#### *Implications for clinical practice*

In breast cancer radiotherapy, cardiac radiation doses have reduced over recent years. Women in this study were irradiated during 1958-2000 and received mean heart doses of ~7 and ~3 Gy in left-sided and right-sided breast cancer respectively. In a systematic review of regimens published 2003-2013, average mean heart doses were 5.4 Gy (range <0.1-28.6) in 398 left-regimens and 3.3 Gy (range 0.4-21.6) in 45 right-regimens.<sup>11</sup>

Nowadays, most women irradiated for breast cancer have tangential radiotherapy after breast-conserving surgery,<sup>11</sup> which is often considered risk-free. However, in some countries, modern left-tangential radiotherapy still delivers several Gy heart dose<sup>11</sup> and the LV apex and mid/distal LAD coronary artery segments are still in the radiation fields for some women.<sup>12</sup> In our study, the left/right ratios for injury to these segments from tangential radiotherapy after breast-conserving surgery were ~3 for the LV apex and ~6 for the mid/distal LAD segment, indicating that irradiating them causes injury and that, where possible, they should be excluded from fields using cardiac-sparing techniques.<sup>12,13</sup>

In breast cancer radiotherapy, cardiac exposure may increase in the future, as recent studies have shown that internal mammary radiotherapy improves breast cancer survival<sup>25-27</sup> and it is difficult to irradiate the internal mammary chain without incidentally irradiating the heart.<sup>11</sup> Also, some women have unfavourable anatomy



where incidental cardiac irradiation is unavoidable. In Hodgkin lymphoma, lung cancer, and esophageal cancer, the tumour can lie close to the heart,<sup>10,13</sup> rendering it difficult to achieve full tumour dose without exposing the heart. In modern 3-dimensional CT-based radiotherapy planning, doses to small regions e.g. cardiac segments can be modified by changing beam angles or using different techniques, so oncologists may have choice over exposure to individual structures. However, there is lack of consistency in radiotherapy guidelines on which cardiac structures are sensitive to radiation and should therefore be avoided. In breast cancer and lymphoma radiotherapy, this is reflected by differing cardiac dose constraints. For example, in some countries the LAD coronary artery is considered a separate organ-at-risk with more stringent dose constraints than the heart, but not in others.<sup>28–30</sup> We demonstrated associations between radiation dose and injury for both LV and coronary artery segments. Therefore the safest strategy, based on current knowledge, is to minimise dose to all segments.

## **Contributors**

SD, PH, ME, PMcG, CT, KR, MBJ and DC designed the study. PMG carried out the analyses with computing assistance from ZW. FD and CT performed the radiation dosimetry. CC, KR and BG coded the cardiology data. DB abstracted the radiotherapy and cardiology data from each woman's medical notes. EL provided radiation dosimetry advice. ZW, FD and PMcG designed and produced the figures. All writing committee members contributed to the report.

## **Declaration of interests**

All authors declare they have no conflicts of interest in relation to this work.

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The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication. Procedures for accessing the data for this study are available on: <https://www.ndph.ox.ac.uk/about/data-access-policy>

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Table 1: Characteristics of 456 women who underwent radiotherapy for breast cancer and subsequently had a cardiac event, and for whom information was available on the location of the cardiac injury.

Figure 1. Axial CT image at the level of the mid left ventricle illustrating the LV and coronary artery segments.

Figure 2. Spatial distribution of radiation dose in the heart from breast cancer regimens commonly used in different decades for women in the study.

Figure 3. Left ventricular segment injury by radiotherapy technique: Average typical doses to ventricular segments in radiotherapy for left-sided and right-sided breast cancer, and numbers of women with ventricular injury in left-sided and right-sided breast cancer.

Figure 4. Left ventricular segment injury by type of surgery and technique: Average typical doses to ventricular segments in radiotherapy for left-sided and right-sided breast cancer, and numbers of women with ventricular injury in left-sided and right-sided breast cancer.

Figure 5. Coronary artery disease by type of surgery and technique: Average typical doses to arterial segments in radiotherapy for left-sided and right-sided breast cancer, and numbers of women with coronary artery disease in left-sided and right-sided breast cancer.

**Table 1: Characteristics of 456 women who underwent radiotherapy for breast cancer and subsequently had a cardiac event, and for whom information was available on the location of the cardiac injury.**

	Women with documented location of left ventricular injury <sup>*</sup>				Women with documented location of coronary artery disease <sup>*</sup>			
	Left <sup>†</sup>	Right <sup>†</sup>	Ratio left/right (95% CI) <sup>‡</sup>		Left <sup>†</sup>	Right <sup>†</sup>	Ratio left/right (95% CI) <sup>‡</sup>	
<b>Initial information on case-defining event</b>								
Hospital discharge register:								
- myocardial infarction	218	158	1.38	(1.12, 1.69)	40	28	1.43	(0.88, 2.32)
- coronary artery disease	20	9	2.22	(1.01, 4.88)	34	23	1.48	(0.87, 2.51)
Death certificate only	5	4	1.25	(0.34, 4.65)	6	2	3	(0.61, 14.86)
			<i>p for heterogeneity: 0.49</i>				<i>p for heterogeneity: 0.66</i>	
<b>Information documenting location of injury <sup>§</sup></b>								
Angiogram	-	-	-	-	80	53	1.51	(1.07, 2.14)
Electrocardiogram	218	158	1.38	(1.12, 1.69)	-	-	-	-
Echocardiogram	94	80	1.17	(0.87, 1.58)	-	-	-	-
Perfusion	4	3	1.33	(0.30, 5.96)	-	-	-	-
MUGA	2	1	2.00	(0.18, 22.1)	-	-	-	-
Autopsy	37	17	2.18	(1.23, 3.87)	15	4	3.75	(1.24, 11.30)
Ventriculography	1	1	1.00	(0.06, 16.0)	-	-	-	-
			<i>p for heterogeneity: 0.58</i>				<i>p for heterogeneity: 0.10</i>	
			<i>p for difference ECG only versus all other women: 0.64</i>					
<b>Cardiac risk factors documented at time of breast cancer diagnosis</b>								
Previous diagnosis of ischemic heart disease <sup>¶</sup>	21	15	1.40	(0.68, 2.52)	11	6	1.83	(0.68, 4.96)
Any other cardiac risk factor <sup>  </sup>	118	81	1.46	(1.11, 1.95)	38	20	1.90	(1.11, 3.27)
No known risk factor	104	75	1.39	(1.07, 1.91)	31	27	1.15	(0.69, 1.92)
			<i>p for heterogeneity: 0.97</i>				<i>p for heterogeneity: 0.38</i>	
<b>All women <sup>**</sup></b>	243	171	1.42	(1.17, 1.73)	80	53	1.51	(1.07, 2.14)
<i>Average of typical radiation doses to left ventricle/main coronary arteries (Gy)</i>	8.3	0.6	-	-	8.0	0.6	-	-
<i>Mean heart dose (Gy)</i>	6.9	3.2	-	-	6.9	3.2	-	-

\* Ninety one women had evidence of both left ventricular injury and coronary artery disease with ≥70% stenosis.

† Numbers of women with injury following radiotherapy for left-sided and right-sided breast cancer respectively.

‡ Ratio of the number of women with left-sided breast cancer to the number of women with right-sided breast cancer and 95% confidence interval.

§ Some women had information from more than one source. Information on the location of the left ventricular injury for 234 women was obtained from at least one of the following: echocardiogram, myocardial perfusion scan, multiple-gated acquisition (MUGA) scan, autopsy or ventriculography. For the other 180 women information on the location of the injury was available only from electrocardiograms. Of these, 108 had left-sided and 72 had right-sided breast cancer and the ratio left/right was 1.50 (1.11, 2.02)

¶ Women with myocardial infarction or angina cited in their oncology record at the time of breast cancer diagnosis, or for whom ischemic heart disease had been recorded as a primary diagnosis in the hospital discharge register before breast cancer diagnosis.

|| The factors associated with subsequent risk of heart disease in women without a history of ischemic heart disease included factors for which the association was likely to be causal (e.g. current smoker) and factors for which the association was indirect (e.g. history of chronic obstructive pulmonary disease). Further details are given elsewhere<sup>9</sup>.



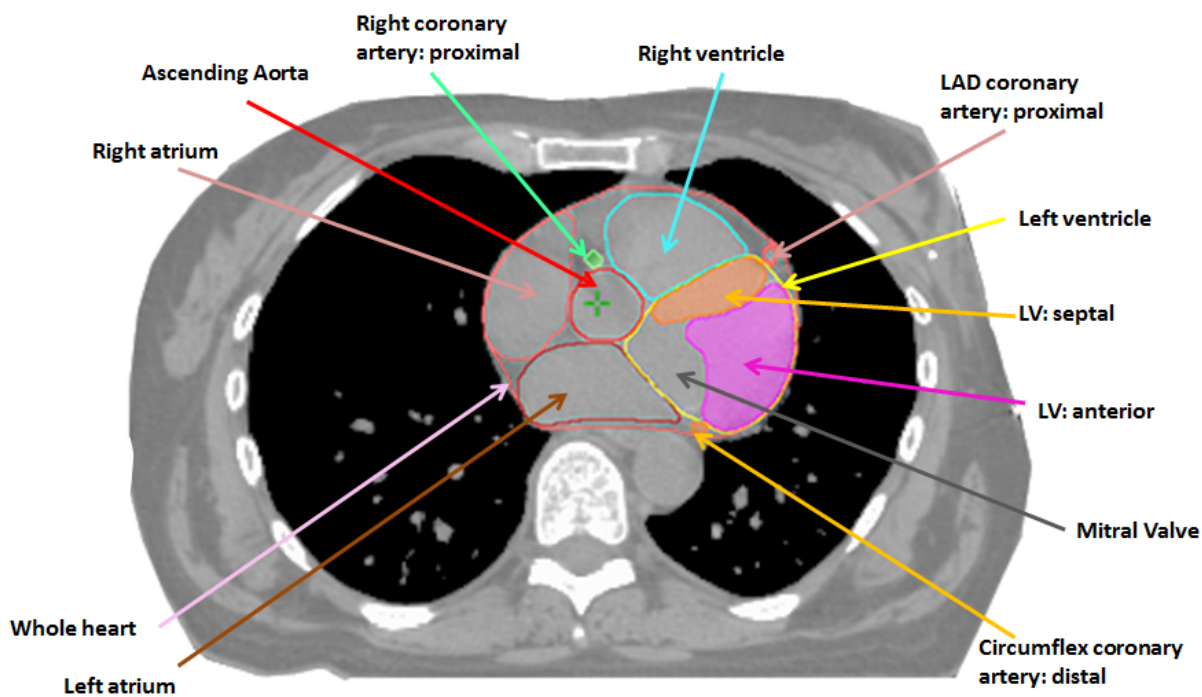
\*\* Additional characteristics of the women are listed on p14 of the appendix.

**Figure 1. Axial CT images illustrating LV and coronary artery segments.**

As is usual in radiotherapy planning the patient's right is on the reader's left.

Abbreviations: LV: left ventricle, LAD: Left anterior descending coronary artery

### A. Level of proximal (superior) left ventricle



### B. Level of mid left ventricle

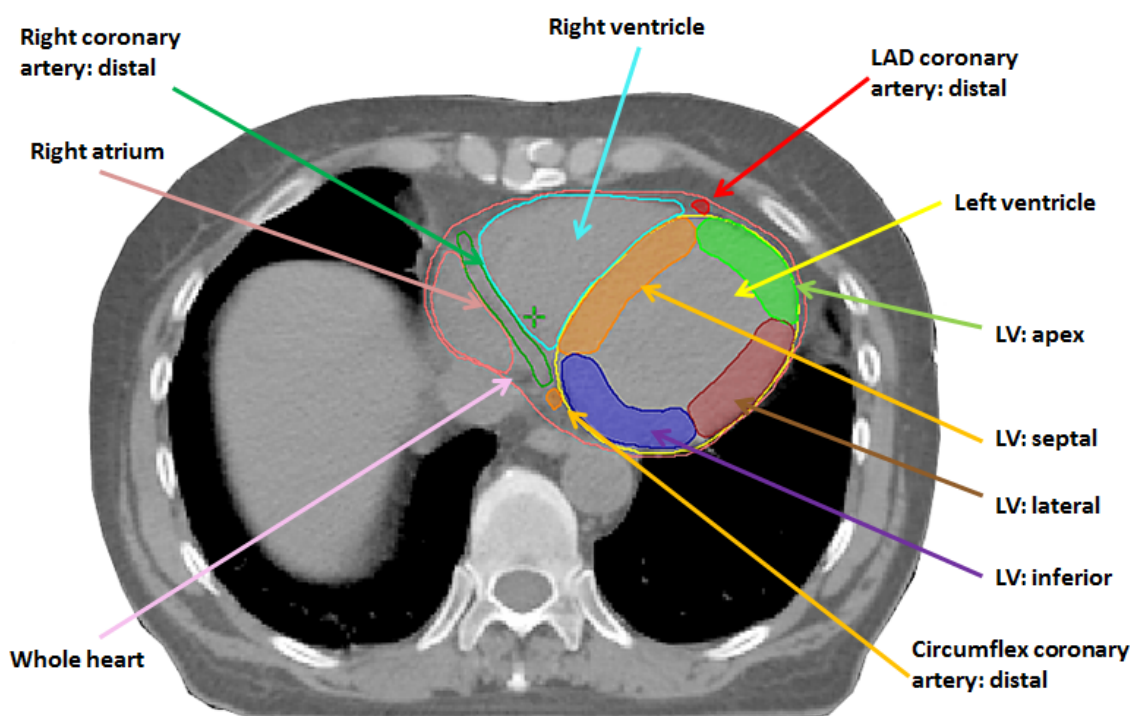
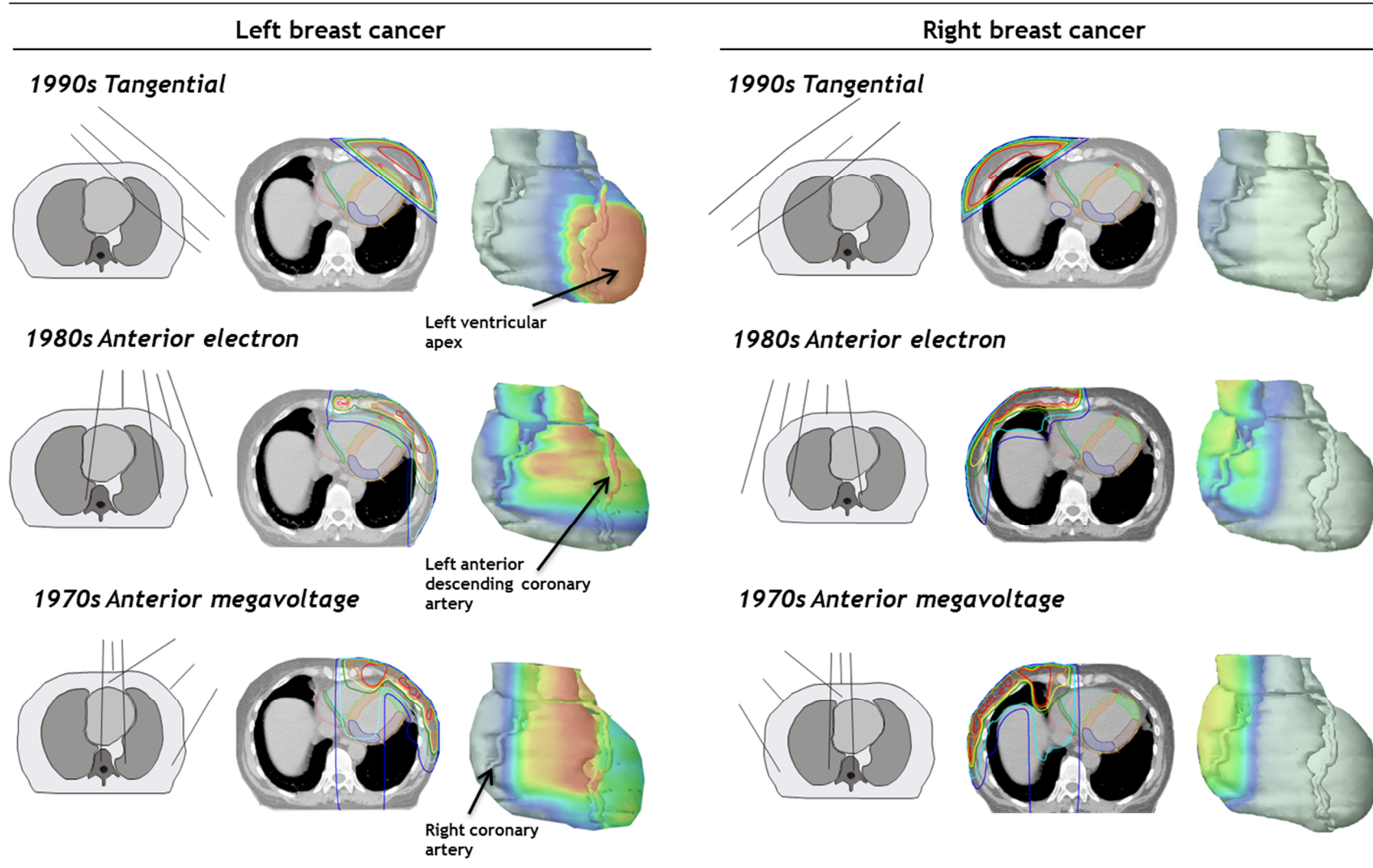




Figure 2. Spatial distribution of radiation dose in the heart from breast cancer regimens commonly used in different decades for women in the study.



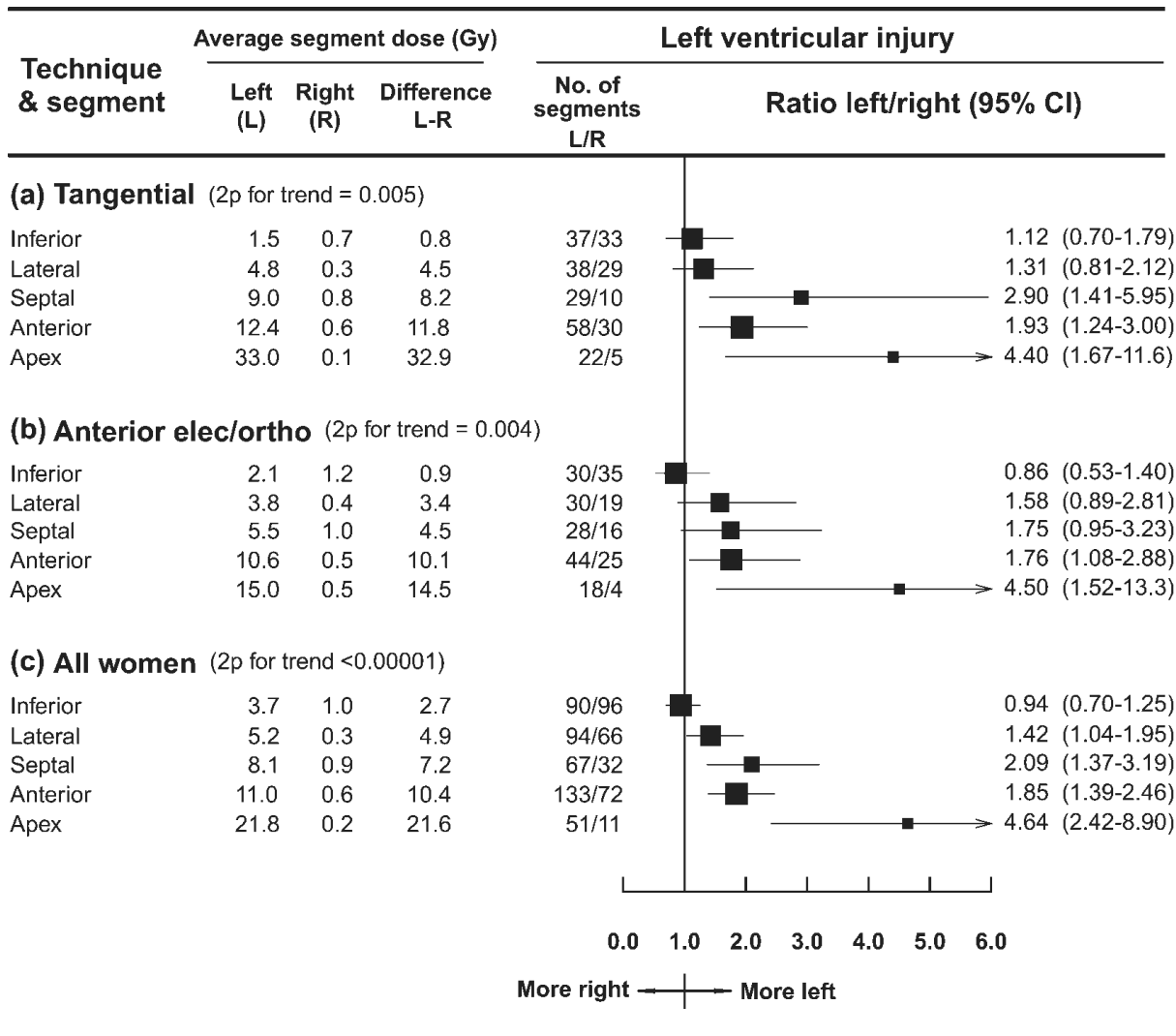
Isodoses (Gy): 50, 48, 44, 40, 25, 10 Field borders were usually 25 Gy

LV segments: Orange=septal, green=apex, brown=lateral, purple=inferior

Anterior electron: Electron field to chest wall and internal mammary lymph nodes, photon field to lateral thorax, axillary and supraclavicular nodes

Anterior megavoltage: Cobalt-60 field to internal mammary lymph nodes, oblique electron field to chest wall projecting to contralateral side

**Figure 3. Left ventricular segment injury by radiotherapy technique: Average typical doses to ventricular segments in radiotherapy for left-sided and right-sided breast cancer, and numbers of women with ventricular injury in left-sided and right-sided breast cancer.**



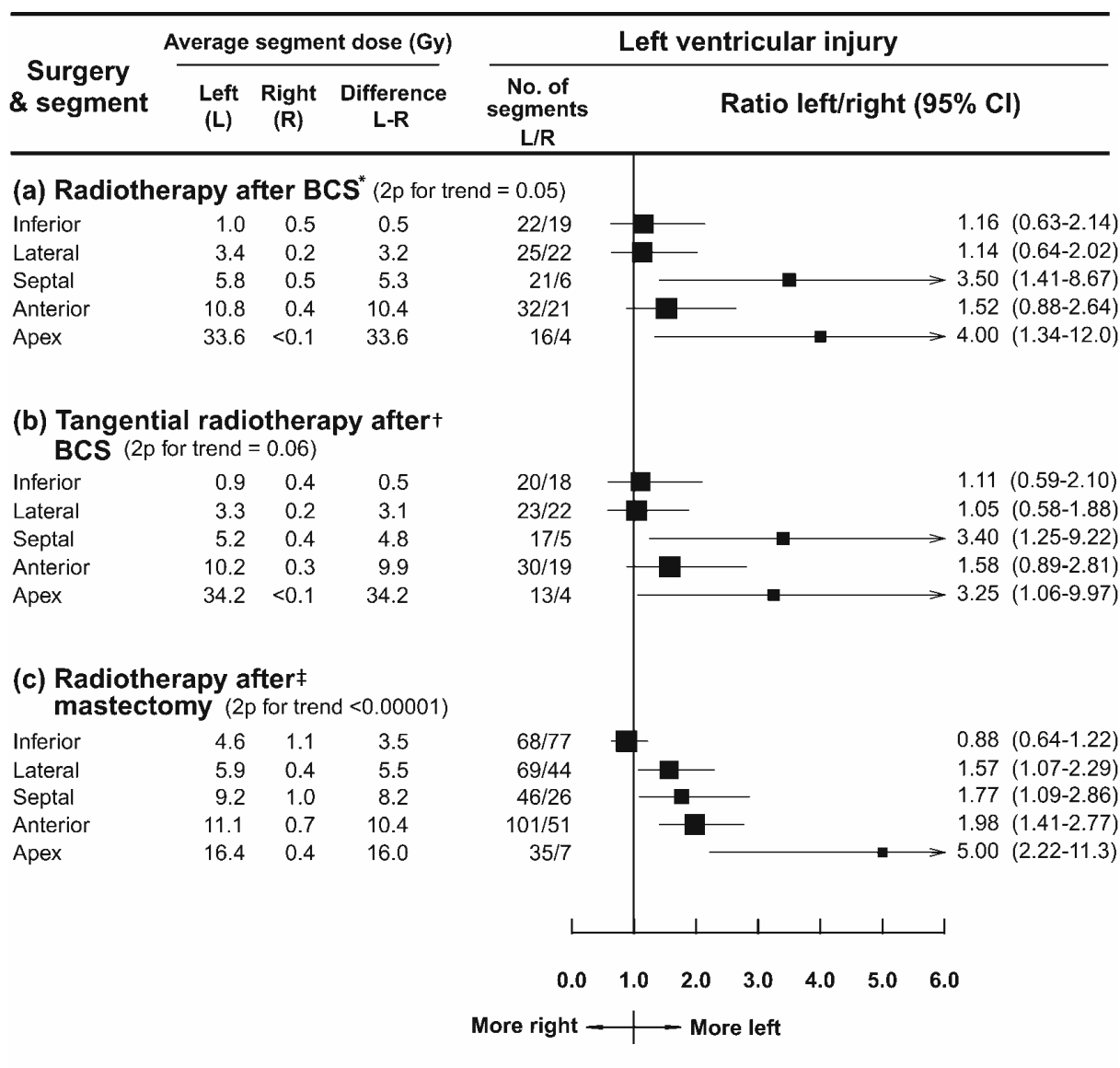
Anterior elec/ortho: Anterior electron/orthovoltage.

In each panel segments are listed in order of difference in the average of the typical segment doses received in left-sided and right-sided breast cancer for women with injury to the segment concerned (i.e. 'Difference L-R').

Some women had injury to more than one segment.

Mean times in years to cardiac events were: (a) Tangential L: 10.8, R: 12.4, (b) Anterior elec/ortho L: 14.2, R: 14.4, (c) All women L:13.7, R:14.5.

**Figure 4. Left ventricular segment injury by type of surgery and technique: Average typical doses to ventricular segments in radiotherapy for left-sided and right-sided breast cancer, and numbers of women with ventricular injury in left-sided and right-sided breast cancer.**



BCS: breast-conserving surgery.

In each panel segments are listed in order of difference in the average of the typical segment doses received in left-sided and right-sided breast cancer for women with injury to the segment concerned (i.e. 'Difference L-R'). Some women had injury to more than one segment.

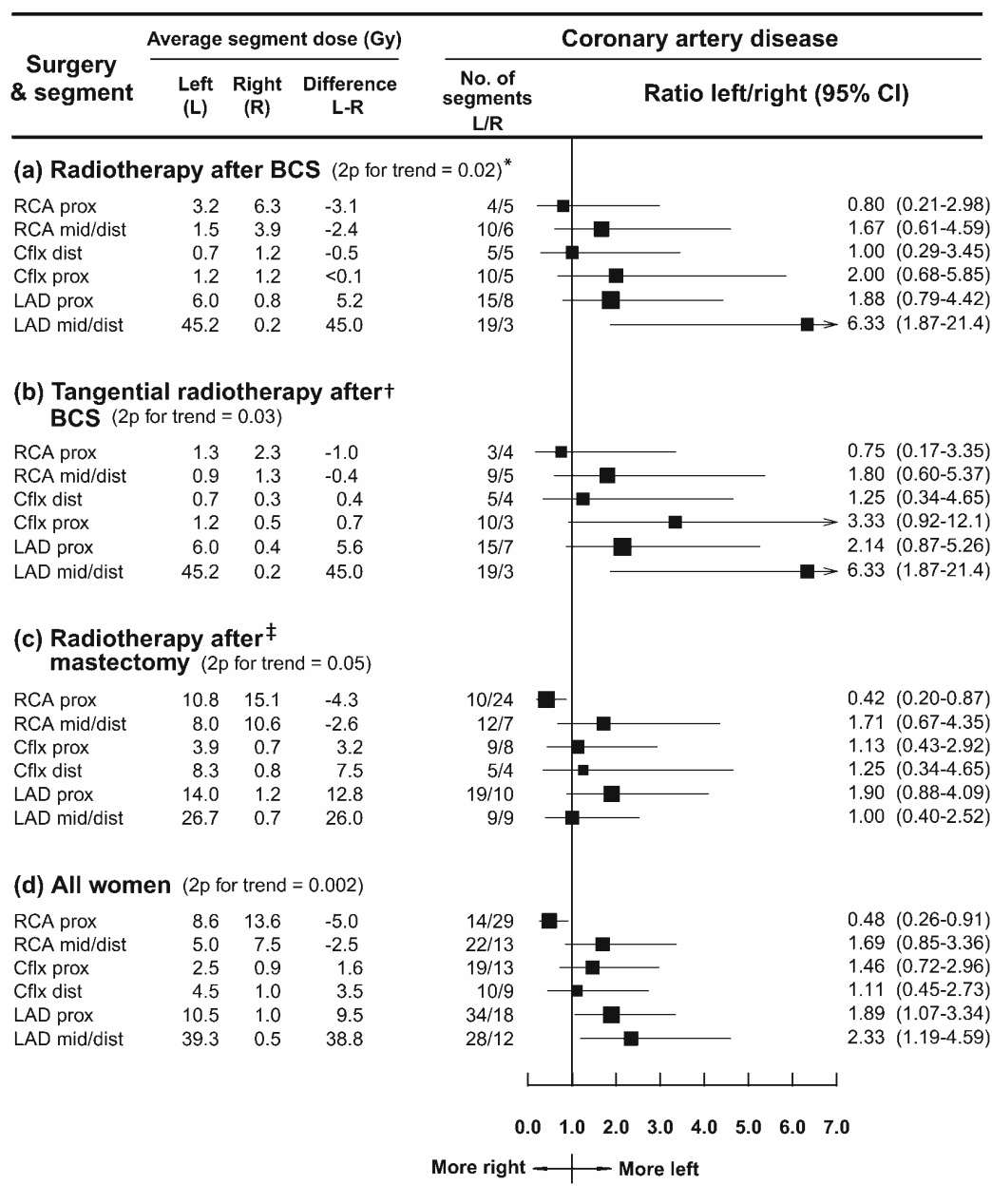
\* Radiotherapy after BCS included tangential in 90/99 women and anterior electron/orthovoltage in 9/99 women.

† Tangents delivered after breast-conserving surgery involved smaller left-minus-right dose differences to most LV segments than tangents after mastectomy because the fields were not as wide, with the medial border typically midline rather than contralateral.

‡ Techniques included tangential in 76/315 women, anterior electron/orthovoltage in 136/315 women, cobalt chain in 66/315 women and anterior megavoltage in 37/315 women.

Mean times in years to cardiac events were: (a) Radiotherapy after BCS L: 7.6, R: 9.6, (b) Tangential radiotherapy after BCS L: 7.5, R: 9.7, (c) Radiotherapy after mastectomy L:15.6, R:16.0.

**Figure 5. Coronary artery disease by type of surgery and technique: Average typical doses to arterial segments in radiotherapy for left-sided and right-sided breast cancer, and numbers of women with coronary artery disease in left-sided and right-sided breast cancer.**



Coronary artery disease was defined as  $\geq 70\%$  stenosis.

BCS: breast-conserving surgery, RCA: right coronary artery, Cx: circumflex, LAD: left-anterior descending artery. prox: proximal, mid/dist: mid/distal, dist: distal.

In each panel segments are listed in order of difference in the average of the typical doses received in left-sided and right-sided breast cancer for women with injury to the segment concerned (ie. 'Difference L-R').

Some women had injury to more than one segment.

128 women had information on diseased coronary artery segment and are included here. 5 additional women had disease with known coronary artery location, but not segment. All 133 women (128+5) are included in figure S6.

\* Radiotherapy after BCS included tangential in 48/53 women and anterior electron/orthovoltage in 5/53 women

† Tangents delivered after breast-conserving surgery involved smaller left-minus-right dose differences to most LV segments than tangents after mastectomy because the fields were not as wide, with the medial border typically midline rather than contralateral.

‡ Techniques included tangential in 16/75 women, anterior electron/orthovoltage in 38/75 women, cobalt chain in 11/75 women and anterior megavoltage in 10/75 women.

Mean times in years to cardiac events were: (a) Radiotherapy after BCS L: 7.0, R: 9.8, (b) Tangential radiotherapy after BCS L: 7.1, R: 9.6, (c) Radiotherapy after mastectomy L: 19.3, R: 17.2, (d) All women L: 13.5 R: 14.7

