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Commentary: A dose–response relationship for radiation-induced heart disease—current issues and future prospects

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There is compelling evidence that ionizing radiation can increase the risk of heart disease. An overview of 63 trials including 32 800 women with early breast cancer[1] found that the death rate from heart disease in women randomized to radiotherapy was 27% higher than that for women randomized to no radiotherapy (SE 7%, $2p = 0.0001$). Irradiated women in these trials received 1–20 Gy mean cardiac dose,[2] depending on the technique used and the laterality of the tumour, typically in about 20 fractions.

Breast cancer radiotherapy techniques have changed since many of the women in these trials were irradiated and mean cardiac doses have reduced. However, the heart still usually receives some dose. A detailed study of cardiac doses from adjuvant tangential breast cancer radiotherapy in 2006 in a major UK radiotherapy centre found that about half the women with left-sided tumours received doses of 20 Gy or more to a small part of the heart, usually including the left anterior descending coronary artery.[3] In addition, most of the heart volume received >1 Gy dose from scattered irradiation in both left- and right-sided breast cancer. In this study of breast cancer patients in 2006, mean dose to the whole heart was 2.3 Gy on average for left-sided breast cancer and 1.5 Gy on average for right-sided breast cancer. The long-term implications of such doses are, as yet, unknown.

Breast cancer is the commonest cancer in women, with around a million new cases diagnosed each year worldwide. Five-year survival is ~80% in many countries and there are now many millions of breast cancer survivors. Radiotherapy has been shown to reduce the risk of recurrence and death from breast cancer. The trials have also shown that radiotherapy can reduce 15-year overall mortality following breast conserving surgery and following mastectomy in node-positive disease,[1] but much uncertainty still remains regarding the long-term overall effect from modern breast cancer radiotherapy. If the relationship between cardiac radiation dose and the long-term risk of heart disease were known, then it would be possible to compare the likely long-term benefit of radiotherapy on the breast cancer with the likely long-term risk of radiation-induced heart disease, and tailor the treatment accordingly. For example, if the risk of radiation-induced heart disease were judged to

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be high for a particular woman, then complex radiotherapy planning techniques might be considered in order to reduce her cardiac dose.

The treatment of early breast cancer illustrates the urgent need to find out more about the long-term risk of heart disease from doses of ionizing radiation in the range 0.5–5 Gy. One of the first suggestions that there might be an appreciable cardiac risk from doses of this magnitude came from the study of long-term survivors of the atomic bombings of Hiroshima and Nagasaki.[4] In this population, risk of death from heart disease increased by 17% per Sv (90% CI 8–20%) following single whole body doses in the range 0–4 Sv, mostly from γ-radiation, for which 1 Sv = 1 Gy. Prompted by this finding, we carried out a systematic review of published epidemiological evidence in which we identified six further studies with doses in the range 0.5–5 Gy where there was no obvious bias or confounding and where there was reasonable power for detecting an effect similar in magnitude to that seen in the atomic bomb survivors.[5] We have now updated this review and a new literature search, carried out along the same lines as previously, has identified three further published studies.[6–8] A fourth study, of workers at British Nuclear Fuels plc (BNFL), has just been published.[9] The BNFL study considers the relationship between mortality from heart disease and cumulative radiation dose in 42 000 monitored radiation workers employed between 1946 and 2002, and followed to 2005. It is by no means the first study of heart disease in monitored radiation workers but, apart from those carried out in Russia, the majority of other studies are based almost entirely on exposures below 0.5 Sv.[5] In contrast, past radiation doses to some BNFL workers at the Sellafield site have been considerable, and an appreciable number of workers received cumulative doses of >0.5 Sv. Therefore, this study may also be informative as regards the risk of radiation-induced heart disease following doses in the range 0.5–5 Gy (or 0.5–5 Sv), and it brings the total number of such studies up to 11.

The results from the 11 potentially informative studies are summarized in Table 1. Five of them, including the BNFL study, find significant positive associations between the risk of heart disease and measures of radiation dose, or reasonable proxy measures such as year of initial employment.[4,6,7,9,10] The remaining six studies, however, find no evidence of any association between radiation dose and risk of death from heart disease[8,11–16] and four of these[8,11–13] are not readily compatible with a positive association. The results of these 11 studies have not been published in a sufficiently uniform format to permit a formal heterogeneity test but it is clear that there is substantial heterogeneity between them. Further evidence of heterogeneity in the dose–response relationship for radiation-induced heart disease comes from the BNFL study itself, as there is significant heterogeneity in the excess relative risk per Sv between different groups of BNFL workers.

These published results are difficult to interpret. It is certainly plausible that there is a causal effect in this dose range. It is also likely that there is appreciable confounding in several of the studies. In the BNFL study there is no significant association between risk of death from lung cancer and radiation dose, indicating that there is unlikely to be confounding with smoking in that study. There is, however, a significant association between the risk of death with a mention of diabetes among the certified causes and radiation dose, suggesting obesity may be confounding the association between radiation dose and heart disease. It is also possible that the risk of radiation-induced heart disease genuinely differs qualitatively between the various study populations (i.e. radiation increases heart disease in some populations and decreases it in others), although at present it is unclear what the relevant risk modifying factors might be. For most of the studies listed in Table 1, there is little prospect of obtaining further information that might provide insight either into potential confounding factors or into possible risk modifying factors.

What are the options for gaining further information? One is to examine the mechanisms of radiation-induced heart disease[17] and several studies focusing on this are in progress. Further follow-up of the randomized trials of women with breast cancer may provide some additional information, but the number of women who have been randomized is limited. There are, however, very large numbers of individuals who have been incidentally exposed to some cardiac radiation during radiotherapy for cancer but who have not been entered into an appropriate radiotherapy trial. For many such individuals, the original radiotherapy treatment chart may still be available so that, with detailed dosimetry based on dose volume histograms, various measures of dose to the whole heart and to different cardiac structures can be estimated.[2] Information on several potential risk-modifying factors is also often available from the patient's medical record. In some circumstances, information on additional factors can also be obtained, either from the patients themselves or from their relatives.

In the randomized trials[1] the breast cancer mortality ratio, irradiated vs not, was 0.88 (SE 0.03) after mastectomy in women with node-positive disease, and 0.83 (SE 0.05) after breast conserving surgery. Both these ratios reflect the causal effect of radiotherapy on breast cancer mortality. Outside the context of a randomized trial, differences between mortality rates in irradiated and nonirradiated individuals will be determined not only by the causal effect of radiotherapy, but also by differences between patients who are selected to receive radiotherapy and patients who are not. Table 2 compares mortality

Table 1 Published epidemiological studies reporting on the association between mortality from heart disease and ionising radiation with doses in the range 0.5–5 Gy (or 0.5–5 Sv) and with good power to detect an association. Based on (5) and updated

Population	Relation between mortality from heart disease and ionising radiation
Studies finding a significant positive association	
Life Span Study of survivors from atomic bombings of Hiroshima and Nagasaki, Japan[4]	RR for heart disease increased by 17% (90% CI 8–26%; $P = 0.001$) per Sv for deaths in period 1968–97, i.e. 23–52 years after exposure.
Radiologic technologists, USA[10]	RR for heart disease, for deaths in period 1983–1997, 1.22, 1.00, 0.98, 1.00 for those starting work <1940, 1940–49, 1950–59, 1960+; P for trend 0.03. Cumulative doses probably up to 2 Gy for those starting before 1950.
Patients irradiated for peptic ulcer, USA[6]	RR for heart disease 1.00, 1.00, 1.23, 1.54, 1.51 at 10+ years after exposure for those with average cardiac doses of 0, 1.6, 2.3, 2.8, 3.9 Gy; P for trend 0.01.
Chernobyl accident emergency workers, Russia[7]	RR for heart disease increased by 41% (95% CI 5–78%; $P = 0.02$) per Gy (no lag).
British Nuclear Fuels, UK[9]	RR for heart disease increased by 70% (90% CI 33–111%; $P < 0.001$) per Sv (with 15-year lag).
Studies not compatible with a positive association based on currently published data	
Radiologists, USA[11]	RR for heart disease compared with all male medical practitioners 1.20 and 1.18 for those registering during 1920–39 and 1940–69, respectively. RRs for cancer calculated on a similar basis were 1.54 and 1.22, respectively. Those registered in early period thought to have had lifetime doses of 2–20 Gy.
Patients with tuberculosis, USA[12]	RR for all circulatory disease: 0.9 (95% CI 0.8–1.00; $P = 0.05$) in exposed vs unexposed. Mean lung dose 0.84 Gy. Mean heart dose likely to be similar.
Radiologists, UK[13]	RR compared with other doctors for all circulatory disease 0.79, 0.83, 0.98, 0.59 for those first registered <1920, 1921–35, 1936–54, 1955–79; P for trend >0.10. RRs for cancer calculated on a similar basis were 1.75, 1.24, 1.12, 0.71; P for trend <0.001. The trend for cancer has been interpreted as an effect of radiation. In the 1920s and 1930s doses may have been ~1 Gy per annum.
Uranium miners, Germany[8]	RR for heart −35% (95% CI −70–0.9%; $P > 0.10$) per Sv for deaths in period 1946–98 (with 5-year lag).
Other studies	
Patients with ankylosing spondylitis, UK[14,15]	RR for circulatory disease excl stroke: RR 0.97 (95% CI 0.70–1.33; $P > 0.10$) in exposed vs unexposed. Mean lung dose 2.5 Gy. Mean heart dose likely to be similar.
Mayak, Russia[16]	RR for all circulatory disease 1.01 (95% CI 0.90–1.15) in those with >1 Gy compared with <1 Gy (no lag).

[a]RR: Death rate ratio.

in irradiated and nonirradiated women registered with early breast cancer in the SEER cancer registries. Radiotherapy is associated with a substantial increase in mortality from breast cancer in women who had a mastectomy, while for breast conserving surgery the opposite is true. This is not surprising, as radiotherapy following mastectomy is recommended only when there is lymph node involvement and, hence, a poorer prognosis, while guidelines recommend radiotherapy for all women given breast conserving surgery, and those who do not receive it are likely to be a highly selected group including, for example, women who become unwell shortly after their surgery but before radiotherapy can be given. What is surprising, however, is that these selection biases are also seen for mortality from all other diseases, including both other cancers and heart disease. Part of the explanation may lie in inaccuracies in the certified cause of death, as for some of these deaths the true underlying cause may, in fact, be breast cancer. This applies particularly to cancers where the death is certified as due to 'cancer of unspecified site'. It seems unlikely,

Table 2 Mortality, irradiated vs not, in women registered with breast cancer in one of the SEER cancer registries, by type of surgery

		Years since diagnosis of breast cancer		
		0–9	10+	All years
Cause of death (ICD9)	**Type of surgery[a]**	RR (95% CI)[b]	RR (95% CI)	RR (95% CI)
Breast cancer (174)	Mast[c]	2.02 (1.97–2.07)	1.58 (1.49–1.68)	1.96 (1.91–2.00)
	BCS[c]	0.61 (0.58–0.65)	0.95 (0.75–1.22)	0.63 (0.60–0.66)
All other diseases (All excl 174, E800–E978)	Mast[c]	1.18 (1.14–1.23)	1.39 (1.32–1.46)	1.26 (1.22–1.30)
	BCS[c]	0.52 (0.50–0.55)	0.94 (0.78–1.12)	0.56 (0.53–0.58)
Cancers of all specified sites other than breast (140–208, 238.6 excl below)	Mast	1.15 (1.06–1.26)	1.35 (1.22–1.49)	1.23 (1.15–1.32)
	BCS	0.72 (0.64–0.82)	0.95 (0.68–1.32)	0.75 (0.67–0.84)
Lung cancer (162.2–162.5,[d] 162.8–162.9) (microscopically confirmed only)	Mast	0.86 (0.67–1.09)	1.81 (1.50–2.18)	1.30 (1.12–1.51)
	BCS	0.99 (0.75–1.31)	1.09 (0.57–2.07)	1.00 (0.78–1.30)
Cancer of unspecified site (159.1, 195–199, 202.3, 202.5–202.6, 203.8)	Mast	1.68 (1.40–2.01)	1.43 (1.09–1.87)	1.59 (1.37–1.85)
	BCS	0.51 (0.37–0.70)	0.84 (0.31–2.23)	0.53 (0.40–0.72)
Heart diseases (390–398, 402, 404, 410–429)	Mast	1.28 (1.20–1.36)	1.67 (1.54–1.82)	1.41 (1.34–1.48)
	BCS	0.50 (0.46–0.55)	0.86 (0.62–1.19)	0.53 (0.48–0.58)
All other diseases	Mast	1.07 (1.00–1.14)	1.19 (1.09–1.29)	1.11 (1.06–1.17)
	BCS	0.46 (0.42–0.50)	1.00 (0.75–1.34)	0.49 (0.46–0.53)
Accident and violence (E800–E978)	Mast	1.25 (1.01–1.55)	0.89 (0.60–1.33)	1.15 (0.95–1.39)
	BCS	0.47 (0.34–0.64)	1.09 (0.24–4.98)	0.49 (0.36–0.67)

[a]Mastectomy (Mast) or breast conserving surgery (BCS). Mastectomy assumed unless BCS specifically recorded.
[b]Mortality rate ratios for women who received radiotherapy compared with women who did not, stratified for age at diagnosis, year of diagnosis, time since diagnosis and race. Details of the SEER data and method of analysis available elsewhere.[18]
[c]In the randomised trials[1] the RR irradiated vs not for mortality from breast cancer was 0.88 (SE 0.03) after mastectomy in women with node-positive disease and 0.83 (SE 0.05) after BCS. The RRs for all cause mortality excluding breast cancer, accident and violence and unknown cause, were 1.14 (SE 0.05) after mastectomy and 1.18 (SE 0.13) after BCS.
[d]i.e. including only deaths where a microscopically confirmed diagnosis of lung cancer occurring after the diagnosis of breast cancer had been recorded in SEER.

however, that the effect can be attributed completely to inaccuracies in the death certification process, as some effect remains even when considering only deaths certified as due to lung cancer and occurring after a microscopically confirmed diagnosis of lung cancer had been registered in one of the SEER cancer registries. Although we do not understand in detail the nature of the selection processes, the resulting biases are clearly much too extreme to be explained by chance. It is particularly surprising that the bias for heart disease is so strong even during the period >10 years after the diagnosis of breast cancer. There are few situations in which selection biases can be demonstrated as clearly as in Table 2 and it useful to bear them in mind in the interpretation of observational studies of the effects of radiation, including those shown in Table 1.

As well as providing a clear illustration of the effects of selection bias, breast cancer also offers a unique opportunity to make inferences that are free of selection bias. This arises because the cardiac radiation doses in women given radiotherapy for left-sided breast cancer are usually larger than the cardiac radiation doses in women given radiotherapy for right-sided breast cancer.[18] In the SEER registry data, the proportions of women with left-sided and with right-sided breast cancer who received radiotherapy across many categories of stage, calendar year, tumour location, age and race were virtually identical[18] suggesting that, at least in this population, breast cancer laterality has in the past played little part in determining who should be given radiotherapy. Figure 1 shows that in the breast cancer patients who were not treated with radiotherapy the subsequent risk of heart disease was independent of tumour laterality, while for irradiated women the heart disease mortality ratio, left-sided vs right-sided, increased with increasing time since diagnosis (i.e. with increasing time since irradiation). The increase is specific to heart disease, as for mortality from all other known causes the mortality ratio, left-sided vs right-sided, is close to unity in both irradiated and nonirradiated women. This suggests that, in this population the increasing trend in the mortality ratio left-sided vs right-sided for heart disease shown in Figure 1 is a causal effect of radiotherapy. It also suggests that in other populations of women irradiated for breast cancer, subsequent patterns of

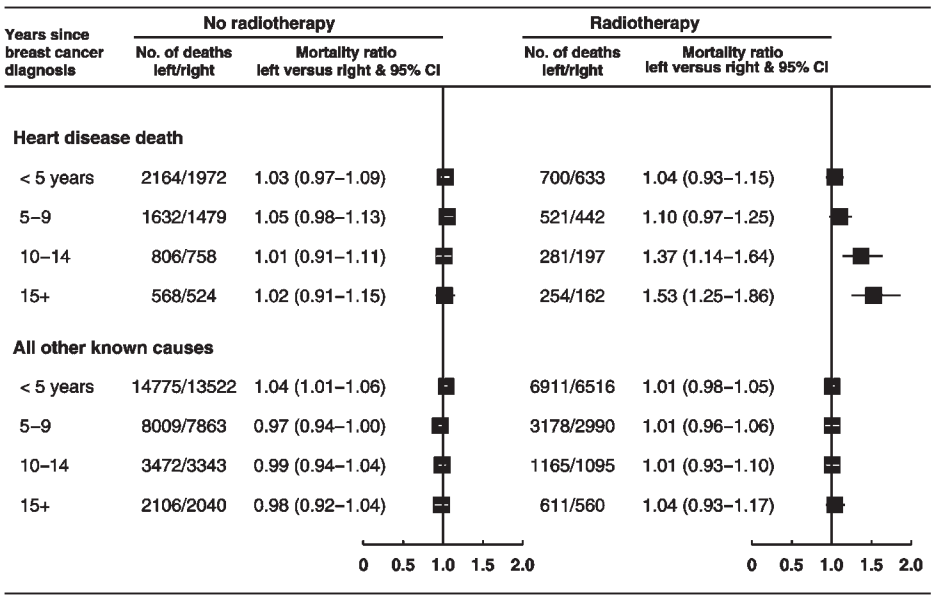

Figure 1 Left- vs right-sided breast cancer: subsequent mortality ratios by radiotherapy status, cause, and years since diagnosis in 300 000 women with breast cancer and registered with the SEER cancer registries (based on reference 18)

heart disease can, when used in conjunction with information on breast cancer laterality and detailed dosimetry, provide insight into the dose–response relationship for radiation-induced heart disease that is as credible as randomized evidence.[19] At least one study designed using these ideas, and including women with a wide range of cardiac doses over a period of >30 years, is currently underway.[20] The first results are expected in 2010 and can be expected to provide the basis of dose–response relationship for radiation-induced heart disease that will be useful in both clinical practice and radiological protection.

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