

standard. With respect to the population groups, we noted in our manuscript the heterogeneity in definitions of East Asians used in the various areas that we studied, but to our knowledge more precise data were not available.

Many of the potential difficulties in data completeness, accuracy and representativeness pertain not only to India but also to Singapore, the UK and the United States. As well as showing possible differences that may be present in cancer rates in different countries, we wanted to highlight the need to improve cancer research among East Asians in India as well as places where substantial migration has occurred. Such ecological studies have provided clues for further study of certain cancers and/or exposures. Thus, we attempted to gather and analyse the best data available and interpret the findings subject to a number of caveats. We feel that a particular strength of our analysis was the presentation of data for a wide range of cancers, revealing a variety of patterns by gender, cancer and geographical area that could be considered in light of potential diagnostic and reporting biases as well as suggesting real differences in risk that might be of etiological significance.

We appreciate the Commentary on our article provided by Dr Sankaranarayanan, who agreed that difficulties may be encountered but that migration studies may provide important clues to the role of environmental and ethnic factors in disease etiology and stimulate further in-depth epidemiologic studies and cancer control interventions.⁶ We agree that

additional research is needed to document the incidence patterns, especially in rural areas of India. It was our hope that our analyses would reveal incidence patterns that would provoke thoughtful discussion and stimulate additional study on the role of environmental and lifestyle factors as well as possible diagnostic and screening practice differences and thus further our understanding of cancer causation and ultimately its prevention.

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Comments: The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946–2005

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The study of McGeoghegan *et al.*¹ documents statistically significant positive trends of mortality risk for circulatory disease, as well as various related end-points (ischaemic heart disease, acute myocardial infarction, stroke, chronic ischaemic heart disease, diabetes) with radiation dose in an important worker cohort. However, there are a number of reasons for

caution in interpreting the findings as representing causal associations. The excess risk per unit dose found is rather stronger, by about a factor of four, than that observed in the Japanese A-bomb survivors. For example, McGeoghegan *et al.*¹ document an excess relative risk (ERR) in relation to all circulatory diseases (ICD9 390–438, 440–459) of 0.54 Sv⁻¹ (90% CI 0.30–0.82) for stroke (ICD9 430–438) of 0.66 Sv⁻¹ (90% CI 0.17–1.27) (Table 1), whereas Preston *et al.*² document an ERR for heart disease (ICD9 390–429)

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Table 1 Excess relative risks (per Sv) of cardiovascular disease in published low dose (<5 Sv) epidemiological datasets with estimated average radiation dose to the heart and for which quantitative risk assessment is possible (reproduced in part from Little *et al.*³)

Data	Ref.	Average heart/brain dose (range) (Sv)	Numbers in cohort (person years follow-up)	Endpoint (mortality unless otherwise indicated)	Excess relative risk Sv ⁻¹ (and 95% CI)
Japanese atomic bomb survivors					
Mortality	2	0.1 (0–4) ^a	86 572 (1 697 861)	Heart disease, 1968–97 (ICD9 390–429)	0.17 (0.08 to 0.26) ^{a,b}
				Stroke, 1968–97 (ICD9 430–438)	0.12 (0.02 to 0.22) ^{a,b}
Morbidity	15	0.1 (0–4) ^c	10 339 (NA)	Hypertension incidence, 1958–98 (ICD9 401)	0.05 (–0.01 to 0.10) ^c
				Hypertensive heart disease incidence, 1958–98 (ICD9 402, 404)	–0.01 (–0.09 to 0.09) ^c
				Ischemic heart disease incidence, 1958–98 (ICD9 410–414)	0.05 (–0.05 to 0.16) ^c
				Myocardial infarction incidence, 1964–98 (ICD9 410)	0.12 (–0.16 to 0.60) ^c
				Stroke incidence, 1958–98 (ICD9 430, 431, 433, 434, 436)	0.07 (–0.08 to 0.24) ^c
Low dose radiotherapy and medical diagnostic studies					
Peptic ulcer study	16	1.3 (0.0–7.6)	3719 (92 979)	Coronary heart disease (ICD8 410–414) ^d	0.10 (–0.12 to 0.33)
				Other heart disease (ICD8 400–404, 420–429) ^d	–0.16 (–0.49 to 0.17)
Ankylosing spondylitis	17	0.14 (0.0–4.80) ^e 2.49 (0.0–17.28) ^f	14 106 (183 749)	Stroke (ICD7 430–434)	–2.43 (–4.29 to 0.71) ^e
				Other circulatory disease (ICD7 400–429, 435–468)	–0.01 (–0.12 to 0.13) ^f
TB fluoroscopy	18	0.84 ^g (NA)	13 385 (331 006)	All circulatory disease (ICD8 390–458)	–0.11 (–0.20 to –0.01) ^g
Occupational studies					
BNFL workers	1	0.0569 (0 to >0.729)	38 779 (1 081 570)	Ischaemic heart disease (ICD9 NA)	0.70 (0.37 to 1.07) ^b
				Cerebrovascular disease (ICD9 430–438)	0.66 (0.17 to 1.27) ^b
				All circulatory disease (ICD9 390–438, 440–459)	0.54 (0.30 to 0.82) ^b
IARC 15- country nuclear worker study	14	0.0207 (0.0 to >0.5)	275 312 (4 067 861)	Circulatory disease (ICD10 I00–I99, J60–J69, O88.2, R00–R02, R57)	0.09 (–0.43 to 0.70)
				Ischaemic heart disease (ICD10 I20–I25)	–0.01 (–0.59 to 0.69)
				Heart failure (ICD10 I50)	–0.03 (<0 to 4.91)
				Deep vein thrombosis and pulmonary embolism (ICD10 I26, I60–I69, I80, I82)	–0.95 (–1.00 to 9.09) ^h
				Cerebrovascular disease (ICD10 O88.2)	0.88 (–0.67 to 3.16)

Chernobyl emergency workers	19	0.109 (0 to >0.5)	61 017 (NA)	All other circulatory disease (ICD10 R00–R02, R57, I00–I99 excluding I20–I26, I50, I60–69, I80, I82)	0.29 (<0 to 2.40)
				Hypertension (ICD10 I10–I15)	0.26 (–0.04 to 0.56)
Canadian nuclear and other workers	10	0.063 (0.0 to >0.4)	206 620 (NA)	Ischaemic heart disease (ICD10 I20–I25)	0.41 (0.05 to 0.78)
				Other heart disease (ICD10 I30–I52)	–0.26 (–0.81 to 0.28)
				Cerebrovascular disease (ICD10 I60–I69)	0.45 (0.11 to 0.80)
				All circulatory disease (ICD10 I00–I99)	0.18 (–0.03 to 0.39)
UK Atomic Weapons Establishment workers				Circulatory disease (males) (ICD9 390–459)	2.3 (0.9 to 3.7) ^b
				Circulatory disease (females) (ICD9 390–459)	12.1 (–0.4 to 24.6) ^b
	11	0.015 (<0.01 to >0.1)	22 543 (NA)	Circulatory disease (ICD9 390–459)	2.51 (0.01 to 5.56)
UK Atomic Energy Authority workers	13	0.01888 (0 to >0.1)	51 367 (1 371 153)	Ischaemic heart disease (ICD9 410–414)	–0.66 (–1.46 to 0.23)
Mayak workers	20	NA (0 to >1)	9373 (NA)	All cardiovascular disease (ICD9 390–405, 410–438, 440–459)	0.00 (–0.06 to 0.06)
US Oak Ridge workers	12	NA (0 to >0.1)	14 095 (425 486)	Ischaemic heart disease (ICD8 410–414)	–2.86 (–6.90 to 1.18)
German uranium miner study	21	0.041 (0 to >0.3)	59 001 (1 801 626)	All circulatory disease (ICD10 I00–I99)	–0.26 (–0.6 to 0.05) ⁱ
Environmental studies				Heart disease (ICD10 I00–I52)	–0.35 (–0.7 to 0.009) ⁱ
				Cerebrovascular disease (ICD10 I60–I69)	0.09 (–0.6 to 0.8) ⁱ
	22	0.0001 (0 to >0.00016)	32 135 (561 063)	Heart disease (white males)	–274 (–874 to 438)
Three Mile Island study				Heart disease (white females)	–951 (–1433 to –390)

^aAnalysis based on colon dose.^b90% CI.^cAnalysis based on stomach dose, derived from Table 3 of ref. 15 with smoking and drinking in the stratification.^dAnalysis excluding highest dose group (3.1–7.6 Gy).^eBased on brain dose.^fBased on heart dose.^gBased on lung dose.^hEstimate derived from log-linear model, evaluated at 1 Sv.ⁱRisk estimates in relation to cumulative whole body external gamma dose.

Table 2 Aggregate excess relative risks (per Sv) of circulatory disease in published low dose (<5 Sv) epidemiological datasets with estimated average radiation dose to the heart and for which quantitative risk assessment is possible, obtained using equations 1 and 2 (using as endpoint mortality from circulatory disease unless otherwise indicated)

Description	Studies included	ERR Sv ⁻¹ (+95% CI)
All occupational and environmental studies excluding McGeoghegan <i>et al.</i> ¹	14, 19, 20, ^a 21, 22 ^b	0.00 (−0.05 to 0.06)
All occupational and environmental studies including McGeoghegan <i>et al.</i> ¹	1, ^c 14, 19, 20, ^a 21, 22 ^b	0.02 (−0.03 to 0.08)
Atomic bomb survivor and medical irradiation studies	2, ^d 15, ^e 16, ^f 17, ^g 18	0.03 (−0.01 to 0.07)
All studies excluding McGeoghegan <i>et al.</i> ¹	2, ^d 14, 15, ^e 16, ^f 17, ^g 18, 19, 20, ^a 21, 22 ^b	0.02 (−0.01 to 0.05)
All studies including McGeoghegan <i>et al.</i> ¹	1, ^c 2, ^d 14, 15, ^e 16, ^f 17, ^g 18, 19, 20, ^a 21, 22 ^b	0.02 (−0.01 to 0.06)

^aAnalysis based on cardiovascular disease.^bAnalysis based on heart disease (males and females separately).^cAnalysis including underlying and contributory causes of death.^dAnalysis based on heart disease and stroke (separately).^eAnalysis based on morbidity from hypertensive heart disease, ischaemic heart disease and stroke (separately).^fAnalysis based on coronary heart disease and other heart disease, excluding highest dose group (3.1–7.6 Gy) (separately).^gAnalysis based on stroke and other circulatory disease (separately).

of 0.17 Sv⁻¹ (90% CI 0.08–0.26) and for stroke (ICD9 430–438) of 0.12 Sv⁻¹ (90% CI 0.08–0.26). Also, the fact that most specific mortality endpoints of non-cancer disease are elevated to a similar extent suggests that there may be bias. As with most other studies of radiation-exposed cohorts (apart from the A-bomb survivors), there is little adjustment for major cardiovascular risk factors, in particular cigarette smoking, diabetes, obesity, blood pressure and blood cholesterol or low density lipoprotein³—only socioeconomic status (a proxy for some of these variables) is adjusted for here, using a crude industrial vs non-industrial classification. Specific occupational factors, in particular stress (e.g. related to shift work, which may well be associated with radiation dose)⁴ also have the potential to confound, and therefore seriously bias the results. It is of interest that there is significant heterogeneity for certain endpoints by employment type and radiation exposure in the study of McGeoghegan *et al.*,¹ which may reflect confounding by some of these factors.

A recent paper systematically reviewed the epidemiological evidence for associations between low and moderate doses (<5 Gy) of ionizing radiation exposure and late occurring cardiovascular disease.³ Risks per unit dose in epidemiological studies varied over at least two orders of magnitude, possibly a result of confounding factors. The paper also reviewed possible biological mechanisms for such low dose effects and indicated that the most likely causative effect of radiation is damage to endothelial cells and subsequent induction of an inflammatory response, although it seems unlikely that this would extend to low dose and low dose-rate exposure.³ However, a role for somatic mutation has been proposed^{5–7} that would indicate a stochastic effect. In the absence of a

convincing mechanistic explanation of epidemiological evidence that is, at present, less than persuasive, the authors concluded that a cause-and-effect interpretation of the reported statistical associations could not be reliably inferred, although neither could it be reliably excluded.³

In comparison even of the lower dose studies summarized in Table 1, a distinction should be made between the acute doses received from radiotherapy and the atomic bombs and the chronic small incremental doses received occupationally. As summarized elsewhere,^{3,8} it is well recognized that the effect at high acute doses is likely to be deterministic and due to a response to cell killing and tissue damage. Therefore studies of radiotherapy patients, even at doses down to 0.5 Gy, and that are reviewed elsewhere,⁹ will not address the issue of mechanisms of any potential effect of small incremental doses, since even at 0.5 Gy there will be quite a lot of cell killing. Low dose chronic exposure will not have the same effect. Even if the same total number of cells are killed, the time span over which this occurs is typically tens of years and their loss is unlikely to be detrimental and will probably be accommodated within the normal patterns of cell turnover and renewal.

We compute an aggregate estimate of ERR across this and other studies using standard statistical methodology. For those studies for which an ERR estimate together with a measure of standard deviation is available, we can compute the best linear unbiased estimate (inverse-variance weighted) of ERR, given by:

$$ERR_{\text{tot}} = \frac{\sum_i ERR_i / SD(ERR_i)^2}{\sum_i 1 / SD(ERR_i)^2} \quad (1)$$

This has standard deviation given by:

$$SD(ERR_{tot}) = \frac{1}{\left[\sum_i 1/SD(ERR_i)^2 \right]^{0.5}} \quad (2)$$

These formulae are used to compute aggregate measures of ERR and associated confidence intervals in Table 2. It should be noted that equation 2 is an exact estimate of the standard deviation. However, when the component distributions are very markedly non-normal (e.g. if they are markedly asymmetric), the resultant scaled linear sum (equation 1) will also be non-normal (e.g. asymmetric) in general. However, as can be seen from Table 1, most estimates of ERR have approximately symmetric confidence intervals about the mean, so it is expected that the scaled sum (equation 1) will also be approximately symmetric about its mean. We apply this formula to a subset of the studies in Table 1, selected so as to be more or less disjoint. For example, we do not include the studies of Ashmore *et al.*,¹⁰ Johnson *et al.*,¹¹ Richardson and Wing¹² and Atkinson *et al.*,¹³ since these are largely subsumed in the IARC 15-country study of Vrijheid *et al.*¹⁴

The results of Table 2 suggest that the aggregate estimate of ERR from all low dose studies excluding the recent study of McGeoghegan *et al.*¹ is 0.02 Sv⁻¹ (95% CI -0.01 to 0.05), and after including it the aggregate estimate of ERR is essentially unchanged at 0.02 Sv⁻¹ (95% CI -0.01 to 0.06). There is significant heterogeneity ($p < 0.01$) in risk between studies, among all groups considered in Table 2. Further analysis in which each study is removed in turn from the "All studies including McGeoghegan *et al.*" group does not substantially alter the aggregate risk estimate, which increased to at most 0.04 Sv⁻¹ (95% CI 0.01, 0.08) (after exclusion of the Massachusetts study¹⁸). Therefore, this analysis suggests that the present paper does little to change the conclusions arrived at in the previous meta-analysis,³ namely that the aggregate low-dose epidemiological data are still only very weakly supportive of a positive trend of cardiovascular disease with dose. As McGeoghegan *et al.* state: 'the tentative nature of biological mechanisms...[and] inhomogeneities in apparent dose-response, mean that the results are not consistent with any simple causal interpretation'.

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