



REVIEW

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REVIEW

Epidemiological studies of UK test veterans: II. Mortality and cancer incidence

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Abstract

An epidemiological study was set up in the 1980s of UK participants in the UK atmospheric nuclear weapons testing programme. A large cohort of test participants was established along with a closely matched comparison or control group. Three analyses of mortality and cancer incidence have been carried out. This review describes the development of the evidence on possible effects on test participants with especial emphasis on the most recent analysis. Other sources of evidence, particularly from studies of other groups of test participants, are also considered. It was concluded that overall levels of mortality and cancer incidence in UK nuclear weapons test participants were similar to those in a matched control group, and overall mortality was lower than expected from national rates. There was no evidence of an increased raised risk of multiple myeloma among test participants in recent years, and the suggestion in the first analysis of this cohort of a raised myeloma risk relative to controls is likely to have been a chance finding. There was some evidence of a raised risk of leukaemia other than chronic lymphatic leukaemia among test participants relative to controls, particularly in the early years after the tests. Whilst this could be a chance finding, the possibility that test participation caused a small absolute risk of leukaemia other than chronic lymphatic leukaemia cannot be ruled out.

1. Introduction

In the 1950s and 1960s the United Kingdom conducted a series of atmospheric tests of nuclear weapons and an associated experimental programme. The nuclear weapons tests took place in Australia and around Christmas Island in the Pacific, while the experimental programme took

Table 1. The UK atmospheric nuclear weapons test programme with numbers of participants at each operation. (Note that men who attended more than one operation appear more than once in the body of this table, but only once in the last line.)

Operation	Location	Date	Number of participants				Total
			RN	Army	RAF	AWE	
Hurricane	Monte Bello Islands	3 Oct. 1952	1076	206	21	95	1 398
Totem	Emu Field	14–26 Oct. 1953	1	11	9	85	106
Mosaic	Monte Bello Islands	16 May–19 June 1956	1134	72	128	49	1 383
Buffalo	Maralinga Range	27 Sep.–21 Oct. 1956	5	194	883	203	1 285
Grapple	Off Malden Island	15 May–19 June 1957	1722	638	1 038	117	3 515
Antler	Maralinga Range	14 Sep.–9 Oct. 1957	60	136	1 156	196	1 548
Grapple X	Off Christmas Island	8 Nov. 1957	597	625	1 011	107	2 340
Grapple Y	Off Christmas Island	28 April 1958	851	1331	1 427	114	3 723
Grapple Z	Christmas Island	22 Aug.–23 Sep. 1958	738	1438	2 016	182	4 374
Brigadoon	Off Christmas Island	25 April–11 July 1962	63	228	395	43	729
MEP ^a	Maralinga and Emu Field	1953–1967	3	174	49	329	555
Other involvements ^b	Australia	Oct. 1952–Aug. 1967	333	630	1 554	47	2 555
Other involvements ^b	Christmas Island	May 1957–June 1964	636	1779	1 533	37	3 985
Total involvements			7219	7462	11 220	1604	27 505
Total participants			6305	5794	8 443	815	21 357

^a MEP = Maralinga Experimental Programme.

^b 'Other involvements' in Australia and Christmas Island refer to involvements at these locations other than at the time of a specific test.

place only at Emu Field and Maralinga in Australia. Details of the tests and the background to the three published reports of an epidemiological study of the test participants are given in the companion article (Kendall *et al* 2004). The reports cited below give detailed comparisons of rates of mortality and the incidence of cancer (including those cancers known to have caused death) between a cohort of test participants and a carefully matched comparison or control group. The analyses considered all causes of mortality taken together and various selected causes and also incidence of all cancers taken together and of various selected cancers. The mortality rates in the test participants were also compared with those of men of the same age from the general population who were born in the same period.

Table 1 summarises the test programme and the number of men involved at each test, by service. As described below, the population studied was essentially the same in the three published analyses and was effectively fixed in the early to mid-1980s. This eliminates the possibility that bias in the selection of the cohort might affect mortality and cancer incidence in the years since that time. The data in table 1 relate to the third analysis. Altogether, systematic searches of contemporary records identified 21 357 men who had taken part in one or more tests. The total number of test involvements in table 1 is higher because individuals who took part in more than one test are shown more than once.

Apart from minor differences in the population studied, there were differences between the three publications in the analyses to which most weight was given. For example, analyses might exclude the first ten years after test participation, in order to allow for a 'latent period' before any radiation induced cancers appeared, or might consider the whole period after first test participation.

This review summarises each of the three published analyses; the original reports (Darby *et al* 1988a, 1988b, 1993a, 1993b, Muirhead *et al* 2003a, 2003b) contain full details. The appendix gives details of the statistical methods used, including definitions of standardised

mortality ratios (SMRs), which were used for comparisons with the general population, and relative risks (RRs), which were used for comparisons between test participants and controls. The appendix also gives a brief outline of the concepts of statistical significance and '*p*-value'. The first two analyses are presented briefly so that the reader can get a feel for the emerging picture about possible harmful effects of test participation. Results for the third analysis, which includes the longest period of follow-up, are presented in more detail. There is also a brief review of studies of other test participants from the United States, New Zealand and Australia. These were of importance in helping to evaluate the results of the UK studies.

2. Interpretation of epidemiological studies

Epidemiological studies are observational rather than experimental in nature and cannot usually give a complete answer to the question of whether exposure to a particular agent has caused a disease. They rather show whether disease levels are or are not raised in the exposed population. When increases are found then further considerations are needed to decide whether chance was responsible for the findings or whether some other factor may be correlated with exposures to the agent under study.

Clearly, epidemiology will have a better chance of detecting an increase in levels of disease if the increase is large and if the natural background level is low. If a study is examining one specific type of disease, then assessment of the statistical significance of the results is fairly simple (see appendix). The SMR or relative risk is either above the expected value or not, and the *p*-value indicates how likely this is to have happened purely through the play of chance. But if many possible diseases are being studied, a complication arises. For example, if SMRs for 20 types of cancer are being investigated, it is more likely than not that at least one of them will appear unusual at the conventional 5% level of significance purely through random effects. Similarly, there is the potential for chance to play a part in elevating or depressing relative risks where random variation in the number of cases may operate in different directions in participants and in controls.

Except for a few rare diseases, epidemiology usually cannot say anything about the cause of a disease in an individual person. It can only detect statistical effects in groups.

The discussion above has assumed that there is no bias involved that will distort the comparisons being made. For example, in the context of the test veterans, it would be very difficult to make any inferences about their disease rates if the population under study had preferentially included those who had developed cancer. The problem could be avoided by including all, or effectively all, the test veterans in the study rather than just a sample, especially if it was volunteered and not obtained by random selection. In this way questions about the representativeness of those included in the study do not arise. But this does not mean that increasing the sample size is automatically beneficial. Adding a biased subgroup to a previously unbiased sample would invalidate a study.

3. Studies of participants in non-UK nuclear weapons tests

The United States conducted a large series of atmospheric nuclear weapons tests involving 230 explosions in 19 operations. In 1978 the United States Department of Defense set up the nuclear test personnel review (NTPR) programme. This set out to establish a register of military personnel who took part in the US tests and their radiation exposure. A number of methods were used to identify participants. One of these was inviting test participants to make themselves known to the NTPR. Details of test involvements notified in this way were checked

against contemporary documents, but nevertheless a risk of selection bias was introduced by accepting self-reported individuals. This risk can be overcome only if a very high proportion of test participants is enrolled. Dates of birth were not always available on the NTPR database. A total of about 210 000 people participated in the US atmospheric nuclear weapons tests. The mean dose was estimated to be about 6 mSv and 99% had total doses less than 50 mSv (DTRA 2003).

This register of test participants has been used for three large studies in which test participants were compared with a matched control group.

- About 70 000 US military personnel who took part in five US test series in the 1950s (Institute of Medicine 2000). The investigators believed that this cohort was 99% complete in the NTPR database. Comparisons were made with a matched group of 65 000 controls. This will be referred to as the 'Five Series Study'. Dates of birth were available in this study so that SMR analyses could be conducted.
- Over 38 000 US Navy personnel who took part in Operation Crossroads, held in 1946 at Bikini Atoll in the Pacific (Johnson *et al* 1996). The NTPR database was estimated to include 93–99% of all such participants. Comparisons were made with a cohort of about 35 000 non-participants (Institute of Medicine 1996). Individual dates of birth were not known.
- About 8500 US Navy veterans who took part in Operation Hardtack I in 1958 in the Pacific (Watanabe *et al* 1995). Comparisons were made with 14 625 Navy veterans who did not participate in any tests. Individual dates of birth were not known.

A study has also been conducted among 528 men from the Royal New Zealand Navy who participated in UK atmospheric nuclear weapons tests in the Pacific (Pearce *et al* 1990, 1997). Comparisons were made with a control group of about 1500 men who were in the RNZN but who did not participate in the tests. As with the US NTPR, individuals were included if they made themselves known to the investigators, but it was believed that overall coverage of those involved was high.

An early study examined the health of Australian participants in the UK atmospheric nuclear weapon tests in Australia. Donovan *et al* (Commonwealth Department of Health 1983) attempted to obtain questionnaire data from 15 364 Australian personnel, thought to have taken part in these tests. A total of 2440 questionnaires were eventually available for analysis. However, difficulties caused by biased response and multiple significance testing made interpretation of the results difficult. More recently, a cohort study of mortality and cancer incidence in Australian participants in the UK nuclear weapons tests in Australia has been set up (Australian Department of Veterans Affairs 2003). This cohort study is being overseen by an independent Scientific Advisory Committee.

The US Five Series Study found a strong 'healthy soldier effect' with an all-causes SMR of 71 and an SMR for all malignancies of 74 compared with rates in the general population, with very similar rates in the referent group. The relative risk for all causes of mortality taken together was elevated to a statistically significant extent amongst the Crossroads participants compared to the control group. The relative risks for all cancers and for leukaemia were above one, but the elevations were smaller than for all causes of death and not significantly greater than one. The authors suggest that the elevation of the all-causes relative risk might be due to some combination of two factors: an unidentified agent other than radiation and self-selection bias. The latter possibility arose because the cohort included some individuals only because they had made their test participation known to the NTPR. The all-causes relative risk was also significantly elevated in the Hardtack I participants compared to controls. The relative risk for all cancers was also above one, but the increase did not reach statistical

significance. The relative risks for cancers of the digestive system and, in particular, for liver cancer were significantly elevated. The authors conclude that ‘the possibility that the veterans who participated in the atmospheric nuclear weapons test may be at increased risk of death from certain cancers cannot be ruled out at this time’.

For the New Zealand study the all-causes SMR was³ 114 (95% confidence interval, CI, 93–140). The all-causes SMR in the control group was 108 (95% CI 95–122). The relative risk was reported as 1.1, not significantly different from one. For all cancers the SMRs in participants and controls were 164 (95% CI 114–227) and 137 (95% CI 110–170) respectively, with a relative risk again not significantly different from one.

Neither the studies of US nor of New Zealand test participants provide compelling evidence that test participation has influenced the induction of cancer generally. However, because of the UK findings, special interest attaches to leukaemia and multiple myeloma, so these diseases are examined in more detail.

In the ‘Five Series Study’, leukaemia mortality was less than the national rate (SMR 74), with some weak (not statistically significant) evidence of a raised risk relative to the matched control group. When chronic lymphatic⁴ leukaemia (CLL), generally accepted as not induced by radiation, was excluded, the findings were similar. No excess of leukaemia was seen in participants in Operation Crossroads or Hardtack I. In contrast, among the New Zealand test participants, there were four leukaemia deaths (SMR = 500, 95% CI 136–1280); in the control group the SMR was 91 (95% CI 11–328). The relative risk in participants compared to the matched control group was 5.6, which was on the borderline of statistical significance. The relative risk for leukaemia incidence was very similar to that for mortality. Thus, there are suggestions from the New Zealand study and, rather uncertainly, from the US Five Series Study of a raised risk of leukaemia.

In the ‘Five Series Study’, mortality from multiple myeloma was slightly less than national rates (SMR 80) and was similar to that in a matched control group. Neither in participants in Operation Crossroads nor Hardtack I was there an excess of multiple myeloma. In the New Zealand test participants, there was one myeloma death compared with 0.3 expected from national rates; the relative risk compared to a matched control group was not significantly different from one. The corresponding findings for myeloma incidence in New Zealand participants were broadly similar to those for mortality. In total, these studies found no evidence of any raised risks of multiple myeloma.

4. The first two published studies of UK test participants

4.1. The first analysis

The first analysis was published in 1988 and covered mortality to the end of 1983 as well as cancer incidence (Darby *et al* 1988a, 1988b). There were 1591 deaths and 671 incident cases of cancer in the test participants and similar numbers in the controls. When broad causes of death were considered, the rates were similar in test participants and in the controls, and usually significantly lower than in the general population. Thus for all causes of death taken together the SMR in participants was 80 (95% confidence interval, CI, 76–84); in controls the SMR was 79 (95% CI 75–83) with a relative risk of 1.01. For all cancers the SMRs were 80 (95% CI 72–88) in test participants versus 83 (95% CI 75–91) in controls with a relative risk of 0.96. However, deaths from accidents and violence were elevated relative to the general

³ The published account of this study gives results to only two significant figures. More precise SMRs with confidence intervals have been calculated from the data in the paper.

⁴ ‘Chronic lymphatic leukaemia’ is now more generally referred to as ‘chronic lymphocytic leukaemia’ (NRPB 2003). We have retained the older name which was used in most published studies.

population in both test participants (SMR 124; 95% CI 111–138) and controls (SMR 121; 95% CI 107–135). But while levels of mortality from accidents and violence were higher than in the general population, they were similar in test participants and the controls (relative risk 1.07; 90% CI 0.93–1.23).

When specific types of cancer were examined, there were significantly higher rates of leukaemia and of multiple myeloma in test participants than in the controls. In comparison with national rates, the levels in test participants seemed unremarkable (SMR 113, 95% CI 71–171, for leukaemia; 111, 95% CI 41–242 for multiple myeloma, based on 22 and six deaths respectively). On the other hand, levels in the controls were low compared with national rates (SMRs of 32, 95% CI 12–69, and 0, 95% CI 0–64, based on six and zero deaths respectively). Such large differences were very unlikely to be due to the play of chance, but no other reason for them was evident.

The only other notable differences were deficits of mortality from cancer of the prostate and of mortality and incidence of cancer of the kidney in test participants relative to the controls. It should be borne in mind that many types of cancer were analysed and some differences might arise by chance alone.

Analyses were carried out of various subgroups, including those in whom exposure to radiation was thought most likely. Unexpectedly, the highest relative risks and standardised mortality ratios were in men not present in the area during a major test and not involved in the minor trials at Maralinga, rather than in those groups where the possibility of radiation exposure seemed greatest.

The authors concluded that:

participation in the nuclear weapons test programme has not had a detectable effect on the participants' expectation of life, nor on their total risk of developing cancer, apart from a possible effect on the risks of developing multiple myeloma and leukaemia (other than chronic lymphatic leukaemia).

4.2. *The second analysis*

The second analysis was published in 1993 and covered mortality to the end of 1990 as well as cancer incidence (Darby *et al* 1993a, 1993b). There were 2753 deaths and 1208 cases of cancer in the test participants. A few individuals were added to the study population for this analysis, largely as a result of information being made available by the US authorities on UK participants in the US operation 'Dominic' in 1962 (known in the UK as operation 'Brigadoon').

During the second analysis, special checks were made to ensure that the low rates of leukaemia and multiple myeloma seen in the first analysis were not a result of incomplete follow-up. These checks included more detailed investigations of deaths and loss to follow-up at the Department of Social Security and of cancer incidence at the National Health Service Central Registers (Darby *et al* 1993b).

The first analysis had included a group of about 1500 men who had had no more potential for exposure than the general population (generally because they had left the test location before the first explosion). In the first report these men were included in the main analysis, although separate results were given for them in some tables. However, in the second and third reports this group was studied completely separately.

Because of the puzzling findings for leukaemia and multiple myeloma in the first analysis, the second analysis included a study of the jobs undertaken by men known to have developed leukaemia (except CLL) and multiple myeloma. However, no strong evidence was found to associate any particular duties with these diseases.

The second analysis, like the first, found that mortality rates from broad causes of death were very similar in test participants and in the controls. Mortality in both groups was generally lower than in the general population. However, in sharp contrast to the first analysis, the rates of leukaemia and of multiple myeloma in the additional seven years of follow-up were slightly (non-significantly) lower in test participants than in controls, and the controls had rates similar to those of the general population. This made it seem more plausible that the low rates of these diseases in controls seen in the first analysis were due to chance. Moreover, a study in the UK of about 400 cases of multiple myeloma and a similar number of controls (Cuzick and De Stavola 1988) had found that roughly equal proportions of cases and controls had served abroad in the Armed Forces in tropical or in semi-tropical areas. This provided evidence against any suggestion that men who had served in such areas should be expected to have low rates of multiple myeloma. However, because the balance of the evidence indicated that radiation induced leukaemia was likely to be concentrated in the period 2–25 years after exposure, and because the relative excess of leukaemia (excluding CLL) in participants compared to the controls was highest in this period, the authors concluded that:

the possibility that test participation may have caused a small risk of leukaemia in the early years after the test could not be ruled out.

4.3. Comments on the earlier analyses by ACHRE

In a 1995 report, the US Advisory Committee on Human Radiation Experiments (ACHRE 1995) suggested that the findings of the first analysis for leukaemia and multiple myeloma might represent an unexpectedly large ‘healthy soldier effect’ or possibly methodological bias. It was, however, stated later that, when the ACHRE report was written, the committee was not aware of the second analysis and that their ‘brief commentary on this study was based on incomplete information’ and ‘it was certainly not our intention to discredit this very well designed study’ (Thomas 1998).

5. The third analysis of UK test participants

5.1. Background

During the mid- to late 1990s, public concern was raised by reports of increased numbers of multiple myelomas among test participants. These reports were based on records for just over 2000 British servicemen in the British Nuclear Test Veterans Association (Rabbitt Roff 1999a, 1999b). This prompted the MoD to commission a third analysis which was conducted under the oversight of an Advisory Group chaired by Professor Nicholas Wald and whose membership is given in the full report of the study. The third analysis had initially been commissioned as a study of multiple myeloma (Hansard 1999). One of the first recommendations of the Advisory Group was that, like the first two analyses, it should consider all causes of mortality and the incidence of cancer. This recommendation was accepted by government (Hansard 2000). Nevertheless, particular attention was given to multiple myeloma in the third analysis.

In all three published studies, references to leukaemia anywhere on a death certificate or cancer registration were taken in preference to other causes in the analyses of cancer incidence. For the third analysis, but not for the first or second, references to multiple myeloma were also taken in preference to other causes.

The third analysis was published in 2003 (Muirhead *et al* 2003a, 2003b) and covered mortality for a further period of eight years, to the end of 1998, as well as cancer incidence. The cohort of test participants and the controls were almost exactly the same as for the second

Table 2. Status of test participants and controls on 1 January 1999. (Note that deaths at age 85 and above (45 deaths in test participants and 55 in controls) are excluded from later analyses.)

Status	Test participants		Controls	
	Number	%	Number	%
Alive	14 560	68.2	15 364	68.8
Dead	4 902	22.9	5 217	23.4
Emigrated	1 882	8.8	1 738	7.8
Lost to follow-up	13	0.1	14	0.1
Total	21 357		22 333	

analysis (21 357 test participants in the third analysis, one fewer than in the second). When follow-up of test participants and of the controls had been completed, as described in the companion review article (Kendall *et al* 2004), the status of test participants and controls at the end of the follow-up period was as shown in table 2. It can be seen that a very high degree of follow-up was achieved and that the status of test participants and of controls was very similar. The analysis included 4857 deaths and 2695 cases of cancer in the test participants.

5.2. Checks with outside organisations

As part of the third analysis, a comparison was made of data on multiple myeloma held by the study investigators and by the investigator at the University of Dundee who had suspected that there was an excess of this disease in the test participants. Full details are given in the report of the study (Muirhead *et al* 2003b). The comparison revealed no additional death certificate or cancer registration (over and above those already known to the study investigators) with multiple myeloma among test participants in the study cohort during the period for which mortality and cancer data were known to be largely complete. Other cases, reported as multiple myeloma on the Dundee list, were not confirmed by death certification or cancer registration. Two of the affected individuals had been awarded war pensions. The authors approached the Pensions Appeals Tribunal for guidance on the basis on which War Pensions are allowed. Under the Service Pensions Order, 1983 (Parliament 1983) in cases where claims for war pensions are made more than seven years after service the individual or his relatives must raise a reasonable doubt based on reliable evidence that there is a link between service and the claimed condition. No clear interpretation of 'reasonable doubt' or of 'reliable evidence' has yet been established. Because every Pensions Tribunal is differently constituted, and each case is decided on its own particular facts as applied to the rather vague concepts of 'reasonable doubt' and 'reliable evidence', no consistent pattern exists of those types of claims for war pensions which are allowed and those which are rejected.

With the agreement of the appropriate authorities, details of the two war pensions cases were given to an independent expert for assessment. He found that one man had myelodysplastic syndrome, which is distinct from multiple myeloma, while the other man appeared to have had a relatively benign multiple myeloma that was unrelated to his death and was therefore not mentioned on his death certificate. This unregistered case of multiple myeloma could not be included in the analysis because no similar method of identification had been sought for unregistered cases in the controls. It is estimated that, during the relevant period, cancer registrations may have been about 10% incomplete, but identical methods had been used to identify incident cases of cancer in the test participants and in the controls, thus enabling a fair comparison between the two groups.

Table 3. Observed deaths and standardised mortality ratios among test participants and controls and relative risks (RR) and confidence intervals (CI) of mortality in test participants compared with controls, over the full follow-up period (up to 1998).

Cause of death	Test participants		Controls		Mortality in test participants relative to controls RR (90% CI)
	Obs	SMR (95% CI)	Obs	SMR (95% CI)	
All causes	4857	89 (86, 91)	5162	88 (85, 90)	1.01 (0.98, 1.05)
Accidents and violence	436	121 (110, 134)	417	116 (105, 128)	1.07 (0.95, 1.21)
Unknown	106		139		0.83 (0.66, 1.03)
All neoplasms	1546	93 (88, 98)	1645	92 (88, 96)	1.01 (0.96, 1.08)
Other diseases	2769	80 (77, 83)	2961	79 (76, 82)	1.01 (0.97, 1.06)
Cancers of tongue, mouth and pharynx	32	118 (82, 169)	40	139 (100, 190)	0.88 (0.58, 1.33)
Stomach cancer	92	78 (63, 96)	92	72 (58, 88)	1.08 (0.83, 1.39)
Liver cancer	24	113 (73, 170)	17	75 (44, 120)	1.54 (0.88, 2.73)
Primary liver cancer	12	98 (51, 171)	13	100 (53, 170)	0.99 (0.47, 2.05)
Lung cancer	480	85 (78, 93)	535	88 (81, 96)	0.97 (0.88, 1.08)
Malignant melanoma	29	165 (112, 239)	27	146 (97, 214)	1.14 (0.71, 1.83)
Non-melanoma skin cancer	2	51 (6, 182)	0	0 (0, 87)	∞ (0.46, ∞)
Prostate cancer	106	115 (94, 139)	97	96 (78, 118)	1.20 (0.94, 1.53)
Bladder cancer	52	95 (72, 126)	34	57 (40, 81)	1.69 (1.15, 2.49)
Kidney cancer	43	106 (77, 144)	63	145 (112, 187)	0.74 (0.52, 1.04)
Multiple myeloma	22	96 (61, 147)	18	73 (43, 115)	1.43 (0.81, 2.54)
Leukaemia	45	98 (72, 131)	33	68 (47, 96)	1.45 (0.96, 2.17)
Leukaemia (2–25 years)	20	123 (75, 189)	6	32 (12, 70)	3.38 (1.45, 8.25)
Leukaemia excluding CLL	40	106 (77, 146)	23	58 (38, 89)	1.83 (1.15, 2.93)
Leukaemia excluding CLL (2–25 years)	18	123 (73, 194)	6	36 (13, 79)	2.99 (1.26–7.41)

The comparison with the University of Dundee also showed that the percentage of confirmed test participants on their list who were in the study cohort was very similar to the previously estimated coverage of test participants (i.e. about 85%). Thus there was no indication that test participants with multiple myeloma were less likely to be included in the study cohort than other men who took part in the test programme.

The accuracy and completeness of diagnoses of haematological neoplasms (leukaemia, multiple myeloma and related diseases) was also assessed against a registry of haematological neoplasms maintained, independently of ONS, by the Leukaemia Research Fund (Cartwright *et al* 1990). The comparison did not suggest any omissions of haematological neoplasms from the study in either test participants or controls. Furthermore, there was good overall agreement between the Leukaemia Research Fund and the study diagnoses. Further details of this intercomparison are given in the full report of the study (Muirhead *et al* 2003b).

5.3. Results

Table 3 compares the mortality by broad cause in participants and in controls over the whole of the follow-up period, i.e. to the end of 1998. Table 3 also gives numbers of observed deaths, SMRs and relative risks for types of cancer which it was thought might be of special interest. With the exception of the leukaemia results for the period 2–25 years after first test involvement, these findings are for the whole of the follow-up period. Results were also calculated excluding the first ten years after first test involvement so as to allow for a possible latent period before any induced cancer might manifest itself, and also to reduce the impact of the 'healthy worker effect'. Findings including and excluding the first ten years of observation are given in the

Table 4. Numbers of incident cancers (I) among test participants and controls, and relative risks (RR) with confidence interval (CI) of incident cancer in test participants compared with controls.

Type of cancer	Test participants I	Controls I	RR	90% CI
All neoplasms	2695	2918	0.99	0.94, 1.03
Tongue, mouth, pharynx	60	76	0.86	0.64, 1.16
Stomach cancer	119	123	1.04	0.83, 1.29
Liver cancer	33	18	2.03	1.21, 3.43
Primary liver cancer	22	13	1.83	0.98, 3.47
Lung cancer	542	615	0.95	0.86, 1.04
Malignant melanoma	56	56	1.09	0.78, 1.51
Non-melanoma skin cancer	333	402	0.88	0.78, 1.00
Prostate cancer	244	216	1.22	1.04, 1.44
Bladder cancer	158	153	1.10	0.91, 1.34
Kidney cancer	71	107	0.71	0.54, 0.92
Multiple myeloma	35	35	1.14	0.74, 1.74
Leukaemia	67	53	1.33	0.97, 1.84
Leukaemia (2–25 years)	29	10	3.17	1.63, 6.31
Leukaemia excluding CLL	49	36	1.41	0.96, 2.09
Leukaemia excluding CLL (2–25 years)	23	6	3.97	1.73, 9.61

report of the third analysis and are generally similar (Muirhead *et al* 2003b). Analyses were also undertaken in which a slightly wider disease grouping was taken for multiple myeloma (Muirhead *et al* 2003b). However, only one extra case fell within the expanded definition and the results differed little.

Table 4 presents numbers of incident cases of malignant disease in test participants and in controls and also relative risks in test participants compared to controls. As with table 3, the whole period of follow-up is considered.

Table 5 compares mortality for the period of the second analysis (to the end of 1990) with that in the further eight years of follow-up, to 1998. Table 6 gives results in similar format to table 5, but for incidence of cancer rather than mortality. The data presented in table 6 for the period to the end of 1990 differ slightly from those published in the second analysis (Darby *et al* 1993a, 1993b), largely because of the late reporting of some cancer cases.

Table 7 gives information on SMRs and relative risks on selected groups of test participants, including those in whom the chance of radiation exposure was thought to be greatest. Table 8 compares mortality in those taking part in Australian tests with those taking part in Pacific tests. Table 9 compares the mortality in independent responders in the period during which these individuals were being notified to the researchers to their mortality afterwards. Table 10 presents results for a group of 1520 men who satisfied the criteria for test participation but who had no more potential for exposure than the general population.

5.4. Discussion

5.4.1. General patterns of mortality and cancer incidence. As with the first two analyses, table 3 shows that mortality rates in both test participants and controls were lower than in men of the same ages in England and Wales for all causes of death, for all cancers and for all other diseases. Risks of mortality in test participants compared to controls were almost identical for each of these broad causes of death (all 1.01, table 3), as was the risk for test participants

Table 5. SMRs and observed numbers of deaths (obs) among test participants and controls, with relative risks (RR) and confidence intervals (CI) of mortality among test participants compared with controls, for selected causes of death and by calendar period.

Cause of death	Up to 31 Dec. 1990			1 Jan. 1991–31 Dec. 1998		
	Test participants SMR (95% CI) (obs)	Controls SMR (95% CI) (obs)	RR (90% CI)	Test participants SMR (95% CI) (obs)	Controls SMR (95% CI) (obs)	RR (90% CI)
All causes	84 (81, 88) (2768)	84 (81, 87) (2959)	1.00 (0.96, 1.05)	95 (91, 99) (2089)	93 (89, 97) (2203)	1.03 (0.98, 1.08)
Accidents and violence	122 (110, 136) (374)	119 (107, 131) (359)	1.06 (0.94, 1.21)	116 (89, 149) (62)	102 (78, 133) (58)	1.13 (0.82, 1.55)
All neoplasms	82 (77, 89) (761)	86 (80, 92) (850)	0.96 (0.88, 1.05)	106 (98, 113) (785)	100 (93, 107) (795)	1.07 (0.98, 1.17)
All diseases other than neoplasms	76 (73, 80) (1565)	75 (71, 79) (1665)	1.02 (0.96, 1.08)	86 (81, 91) (1204)	86 (81, 90) (1296)	1.01 (0.94, 1.08)
Cancer of mouth, tongue and pharynx	74 (37, 133) (11)	139 (89, 213) (22)	0.56 (0.28, 1.08)	171 (108, 265) (21)	138 (82, 218) (18)	1.26 (0.71, 2.25)
Liver cancer	126 (65, 220) (12)	49 (16, 114) (5)	2.58 (0.97, 7.23)	103 (53, 179) (12)	96 (50, 186) (12)	1.11 (0.53, 2.34)
Primary liver cancer	102 (41, 209) (7)	68 (22, 159) (5)	1.41 (0.47, 4.38)	93 (30, 217) (5)	140 (60, 275) (8)	0.71 (0.24, 2.04)
Lung cancer	73 (65, 83) (242)	85 (75, 95) (303)	0.87 (0.76, 1.01)	102 (90, 116) (238)	93 (82, 106) (232)	1.10 (0.94, 1.29)
Bladder cancer	106 (72, 154) (29)	37 (18, 66) (11)	2.85 (1.51, 5.47)	85 (55, 129) (23)	79 (51, 120) (23)	1.13 (0.67, 1.91)
Multiple myeloma	77 (35, 147) (9)	48 (17, 104) (6)	1.90 (0.71, 5.23)	114 (61, 195) (13)	98 (51, 172) (12)	1.21 (0.58, 2.53)
Leukaemia	100 (68, 145) (29)	56 (33, 90) (17)	1.75 (1.01, 3.06)	94 (53, 152) (16)	87 (50, 142) (16)	1.12 (0.59, 2.13)
Leukaemia excluding CLL	109 (73, 160) (27)	58 (33, 96) (15)	1.84 (1.02, 3.33)	102 (54, 174) (13)	59 (25, 116) (8)	1.81 (0.80, 4.18)

Table 6. Number of incident cancers among test participants and controls, and relative risks (RR) and confidence interval (CI) of incident cancer in test participants compared with controls for selected types of cancer, by calendar period.

Type of cancer	Up to 31 Dec. 1990			1 Jan. 1991–31 Dec. 1998		
	Test participants	Controls	RR (90% CI)	Test participants	Controls	RR (90% CI)
All neoplasms	1326	1456	0.97 (0.91, 1.03)	1369	1462	1.01 (0.95, 1.07)
Cancers of tongue, mouth and pharynx	30	37	0.88 (0.57, 1.35)	30	39	0.84 (0.55, 1.29)
Cancer of liver	15	7	2.31 (1.00, 5.48)	18	11	1.84 (0.92, 3.71)
Primary liver cancer	9	5	1.88 (0.67, 5.53)	13	8	1.80 (0.80, 4.14)
Lung cancer	283	340	0.89 (0.78, 1.02)	259	275	1.01 (0.87, 1.17)
Non-melanoma skin cancer	137	187	0.78 (0.64, 0.95)	196	215	0.97 (0.82, 1.15)
Bladder cancer	81	67	1.27 (0.95, 1.69)	77	86	0.97 (0.74, 1.28)
Multiple myeloma	17	10	2.05 (0.99, 4.30)	18	25	0.79 (0.45, 1.38)
Leukaemia	37	29	1.31 (0.84, 2.04)	30	24	1.37 (0.86, 2.22)
Leukaemia excluding CLL	30	21	1.46 (0.88, 2.45)	19	15	1.39 (0.74, 2.61)

compared to controls for the incidence of all cancers taken together (0.99; table 4). In contrast, SMRs for accidents and violence continued to be somewhat elevated in both test participants and controls (SMRs of 121, 95% CI 110–134, and 116, 95% CI 105–128, respectively; table 3).

5.4.2. Multiple myeloma. For multiple myeloma, table 5 shows that the relative risk of mortality among test participants relative to controls up to 1990 was 1.90 (90% confidence interval 0.71–5.23). During the extended follow-up period of 1991–98, the relative risk was 1.21 (0.58–2.53). Mortality rates for both participants and controls were not significantly different from the national levels, either during the extended or the full follow-up periods. In terms of incidence (table 6), the relative risk in the latest eight years of follow-up was below one (0.79), though the difference was not statistically significant.

Evidence on the induction of multiple myeloma in the atomic bomb survivors or in those with medical or occupational exposures has been weak (Muirhead *et al* 2003b, UNSCEAR 2000). As noted above, other studies of test participants do not provide convincing evidence of elevated levels of multiple myeloma. Taken overall, the evidence does not indicate a link between participation in the UK nuclear weapons test programme and a risk of multiple myeloma.

5.4.3. Leukaemia. For mortality from leukaemia, excluding chronic lymphatic leukaemia (CLL) which is not thought to be induced by radiation exposure, table 5 shows that the relative risk up to the end of 1990 was 1.84, a statistically significant elevation (90% confidence interval 1.02–3.33). Over the next eight years the relative risk was very similar, 1.81, although, with smaller numbers, the elevation was not statistically significant (90% confidence interval 0.80–4.18). Over both periods, the SMRs for test participants were close to national rates (109 and 102), while those for controls were a little low (58 and 59).

The relative risks for incidence of leukaemia (excluding CLL) in test participants relative to controls over both periods were lower than those for mortality (table 6); in neither period was the relative risk statistically significantly raised.

For the time period 2–25 years after first test participation the relative risk in test participants was elevated relative to controls, both in the case of mortality and of incidence

Table 7. Standardised mortality ratios (SMR) and observed deaths (O) among test participants and relative risks (RR) of mortality among test participants compared with controls. For leukaemia the whole follow-up period and the period 2–25 years after start of the first test participation are considered. (Note: * $0.05 > p > 0.01$; ** $0.01 > p > 0.001$; *** $p < 0.001$.)

Type of cancer	Test participants at a major operation (15 634 men)		Test participants in groups identified by MOD as liable to exposure to radiation (759 men) (group A)		Test participants employed by AWE or directly involved in the minor trials at Maralinga ^a (1041 men) (group B)		Test participants in groups A and B, plus other men with a recorded dose greater than zero (2649 men)		Other test participants (5164 men)		All test participants (21 357 men)	
	SMR (O)	RR (90% CI)	SMR (O)	RR (90% CI)	SMR (O)	RR (90% CI)	SMR (O)	RR (90% CI)	SMR (O)	RR (90% CI)	SMR (O)	RR (90% CI)
Leukaemia: whole follow-up period	95 (33)	1.35 (0.87, 2.10)	47 (1)	0.72 (0.04, 4.81)	123 (4)	2.38 (0.43, 16.54)	83 (6)	1.21 (0.45, 3.11)	109 (11)	1.72 (0.89, 3.25)	98 (45)	1.45 (0.96, 2.17)
Leukaemia: 2–25 years	85 (10)	2.03 (0.77, 5.50)	142 (1)	6.02 (0.35, 42.11)	89 (1)	3.62 (0.04, 264.3)	81 (2)	2.71 (0.29, 15.68)	221* (9)	7.63 (2.73, 21.83)	123 (20)	3.38 (1.45, 8.25)
Leukaemia excluding CLL: whole follow-up period	106 (30)	1.72 (1.04, 2.84)	59 (1)	0.82 (0.05, 5.79)	159 (4)	2.69 (0.44, 24.50)	105 (6)	1.47 (0.51, 4.00)	108 (9)	2.12 (1.00, 4.39)	106 (40)	1.83 (1.15, 2.93)
Leukaemia excluding CLL: 2–25 years	85 (9)	1.81 (0.67, 5.02)	165 (1)	6.02 (0.35, 42.11)	105 (1)	3.62 (0.04, 264.3)	93 (2)	2.71 (0.29, 15.68)	221 (8)	7.01 (2.43, 20.59)	123 (18)	2.99 (1.26, 7.41)
Multiple myeloma: whole follow-up period	86 (15)	1.21 (0.64, 2.29)	87 (1)	1.01 (0.05, 7.63)	167 (3)	2.08 (0.34, 14.95)	154 (6)	2.16 (0.74, 5.95)	121 (6)	1.61 (0.63, 3.91)	96 (22)	1.43 (0.81, 2.54)
All neoplasms except leukaemia and multiple myeloma: whole follow-up period	91 (1110)	0.98 (0.92, 1.05)	59 (49)	0.71 (0.54, 0.92)	74 (96)	1.27 (1.00, 1.62)	76 (212)	0.99 (0.87, 1.14)	92 (322)	1.01 (0.91, 1.13)	92 (1479)	1.00 (0.94, 1.06)
All cancers: Whole follow-up period	92 (1158)	0.99 (0.93, 1.06)	60 (51)	0.71 (0.55, 0.92)	77 (103)	1.31 (1.03, 1.66)	78 (224)	1.01 (0.89, 1.16)	94 (339)	1.03 (0.93, 1.05)	93 (1546)	1.01 (0.96, 1.08)
All causes: whole follow-up period	89 (3683)	1.01 (0.98, 1.05)	74 (211)	0.93 (0.82, 1.05)	74 (334)	1.27 (1.11, 1.44)	75 (725)	1.02 (0.94, 1.09)	87 (1043)	1.00 (0.94, 1.06)	89 (4857)	1.01 (0.98, 1.05)

^a Those in whom undocumented inhalation or ingestion of radionuclides, if any, is most likely to have occurred.

Table 8. Observed deaths, SMRs with confidence intervals, and RRs of mortality in test participants present at UK atmospheric nuclear weapons tests in Australia and the Pacific. For leukaemia the whole follow-up period and the period 2–25 years after the start of the first test participation are considered. For all causes, multiple myeloma and other neoplasms, the whole period is considered.

Cause of death	Participants at Australian tests			Participants at Pacific tests			Mortality rate in Pacific test participants relative to Australian test participants			
	Observed deaths	SMR ^a	95% CI	Observed deaths	SMR ^a	95% CI	RR ^d	90% CI	Probability ^b one sided	Probability ^c two sided
Leukaemia: whole follow-up period	16	84	48, 137	31	103	71, 148	1.17	0.63, 2.21	0.394	0.732
Leukaemia: 2–25 years	7	111	44, 228	13	119	63, 204	0.88	0.35, 2.29	0.492	0.804
Leukaemia excluding CLL: whole follow-up period	13	85	45, 146	29	117	80, 170	1.42	0.71, 2.89	0.237	0.460
Leukaemia excluding CLL: 2–25 years	5	89	29, 207	13	132	70, 226	1.32	0.46, 3.98	0.428	0.787
Multiple myeloma: whole follow-up period	12	122	63, 214	11	75	37, 133	0.62	0.26, 1.44	0.206	0.354
All neoplasms excluding leukaemia and multiple myeloma: whole follow-up period	630	91*	84, 98	917	89***	84, 95	0.90	0.80, 1.00	0.056	0.111
All causes: whole follow-up period	2049	87***	83, 90	3068	88***	85, 91	0.97	0.92, 1.03	0.196	0.392

^a * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ where p is the probability from a two-sided test that the difference between the number of deaths observed and that expected from national rates could have occurred by chance.

^b One-sided test that the RR is greater than unity (if estimated to be greater than or equal to one), or less than unity (if estimated to be less than one).

^c Two-sided test that the RR is different from unity.

^d Participants who attended both Pacific and Australian tests are excluded (260 deaths in total).

Table 9. Observed deaths (O) and standardised mortality ratios (SMR) with 95% confidence intervals (CI) among independent responders known at the time of the previous analysis, for selected causes of death, by calendar period.

Cause of death	Calendar period up to 28 Feb. 1993		Calendar period 1 March 1993 to 31 Dec. 1998	
	O	SMR(CI)	O	SMR (CI)
All causes	115	163 (135, 197)	42	139 (101, 189)
Accidents and violence	1	14 (0, 77)	2	259 (31, 935)
All neoplasms	64	318 (246, 408)	16	151 (86, 245)
Other diseases	48	112 (83, 149)	23	122 (79, 185)
Multiple myeloma	2	763 (92, 2755)	0	0 (0, 2251)
Leukaemia	2	302 (36, 1088)	2	832 (100, 3004)
Leukaemia excluding CLL	2	349 (42, 1258)	1	557 (14, 3103)

Table 10. Observed deaths and standardised mortality ratios among men with no more potential for exposure to radiation than the general population and relative risks (RR) and confidence intervals (CI) of mortality in these men compared with controls, over the full follow-up period (up to 1998).

Cause of death	Obs	SMR (95% CI)	RR (90% CI)
All causes	348	92 (82, 102)	1.03 (0.94, 1.13)
Accidents and violence	32	125 (86, 178)	1.17 (0.84, 1.62)
Unknown	7		0.75 (0.36, 1.50)
All neoplasms	112	96 (79, 116)	1.03 (0.87, 1.22)
Other diseases	197	83 (72, 96)	1.02 (0.90, 1.16)
Cancers of tongue, mouth and pharynx	4	207 (56, 531)	1.64 (0.58, 4.17)
Stomach cancer	14	173 (94, 290)	2.36 (1.39, 3.95)
Liver cancer	3	196 (40, 571)	2.69 (0.74, 8.39)
Primary liver cancer	1	113 (3, 628)	1.08 (0.07, 6.45)
Lung cancer	31	80 (55, 114)	0.87 (0.63, 1.19)
Malignant melanoma	0	0 (0, 293)	0.00 (0.00, 2.22)
Non-melanoma skin cancer	0	0 (0, 1389)	No inference possible
Prostate cancer	3	49 (10, 142)	0.52 (0.16, 1.48)
Bladder cancer	2	54 (7, 194)	0.92 (0.19, 3.30)
Kidney cancer	1	134 (1, 191)	0.25 (0.02, 1.36)
Multiple myeloma	1	61 (2, 341)	0.80 (0.05, 4.64)
Leukaemia	4	122 (33, 312)	1.99 (0.69, 5.15)
Leukaemia (2–25 years)	1	92 (0, 513)	2.18 (0.13, 14.69)
Leukaemia excluding CLL	3	112 (23, 326)	2.23 (0.63, 6.72)
Leukaemia excluding CLL (2–25 years)	1	101 (0, 563)	2.18 (0.13, 14.69)

(tables 3 and 4). This period was chosen because of evidence that any radiation induced leukaemia would be largely expressed in this period (Darby *et al* 1987, Weiss *et al* 1995). However, analysis of leukaemia incidence among the Japanese atomic bomb survivors indicates that while the radiation risks are mostly expressed within 25 years of childhood exposure, the decline in risk over time is less pronounced following exposure in adulthood (Preston *et al* 1994). Thus radiation risks may persist more than 25 years after adult exposures, although at a lower level than in the earlier period.

Studies of the atomic bomb survivors and of nuclear workers are consistent with an association between radiation exposure and leukaemia (NRPB 2003, Muirhead *et al* 1999). As noted above, there is also some evidence from studies of other test veterans of elevated levels of leukaemia. Taken overall, the evidence indicates that the possibility that test participation

has caused a small absolute risk of leukaemia other than CLL cannot be ruled out and that, whilst the evidence for any risk appears to have been strongest in the early years after the tests, a small risk might have persisted in more recent years.

5.4.4. Other cancers. The tables also show results for other specific types of cancer. These must be interpreted with caution because over 20 types of cancer were investigated and, as discussed above, it must be expected that a few statistically significant results will arise purely by chance.

In comparisons of mortality with national rates for the period up to 1998 (table 3), significant excesses were observed for cancer of the tongue, mouth and pharynx (among controls), malignant melanoma (among participants) and kidney cancer (among controls). There were also statistically significant deficits of cancer of the stomach (both participants and controls), lung cancer (both participants and controls), non-melanoma skin cancer (controls), and bladder cancer (controls). Note that mortality from non-melanoma skin cancer is very much lower than incidence and that the numbers of deaths are small.

There had been three types of cancer for which the second analysis had left a suggestion of excesses or deficits in test participants relative to the controls. These were non-melanoma skin cancer, bladder cancer and liver cancer. For incidence of non-melanoma skin cancer there had been a significant deficit in test participants (table 6) while for mortality from cancer of the bladder there had been a suggestion of an excess (table 5). In both instances, the relative risk over the subsequent eight years of follow-up was close to one. Over the whole period of follow-up the deficit of non-melanoma skin cancer in test participants was now no longer statistically significant. The excess of bladder cancer mortality in test participants remained statistically significant (table 3). It seems likely that these are chance findings, rather than reflecting any effect of test participation.

For cancer of the liver, incidence up to the end of 1990 had been higher in participants than in controls at a level which just reached statistical significance (table 6). Over the next eight years, incidence in participants was again higher than in controls, though the elevation was not statistically significant. Many liver cancers arise as secondaries to a primary tumour elsewhere. Any excess of induced liver cancer might therefore be expected to show more clearly in primary liver cancers. However, the relative risks for liver cancers that were specifically specified as primaries were no higher than for the broader category which included liver cancers not specified as primary. Over the whole of the follow-up period, the increase in incidence for the broader category of liver cancers in test participants compared to controls reached statistical significance (table 4). A significant excess of liver cancer has been seen in the survivors of the atomic bombs and in this population radiation is taken to be the likely cause (Cologne *et al* 1999). Other risk factors for liver cancer include alcohol. There is an excess of alcohol related mortality in both test participants and controls relative to the general population (SMRs 147 and 159 respectively, based on the follow-up period (Muirhead *et al* 2003b)). However, the risks in participants are very similar to those in controls (relative risk 0.97; 90% confidence interval 0.75–1.24). Compared with the general population, an elevation in mortality from cirrhosis of the liver (SMR 229) has been reported in test participants and controls from the Navy (Darby *et al* 1990). In view of the large number of cancer types studied and the results for primary liver cancer, the higher incidence of liver cancer in participants relative to controls may be a chance finding.

Two other statistically significant differences in cancer incidence between test participants and controls were observed when the whole of the follow-up period was considered (table 4). Incidence of prostate cancer was elevated in participants while incidence of kidney cancer was elevated in the control group. Chance again seems the most probable explanation.

5.4.5. *Analyses of subgroups of test participants.* In addition to the analyses described above, sub-analyses were carried out to try to identify special groups in whom any risk of test participation, including any undocumented exposure to radionuclides, might have been concentrated. Findings on cancer mortality among participants according to the type of test involvement are given in table 7. Similar results for cancer incidence are given elsewhere (Muirhead *et al* 2003b). Table 7 considers a number of groups of test participants:

- (1) Those involved in one of the major operations.
- (2) Those in groups identified by the MoD as liable to exposure to radiation; see the companion review article (Kendall *et al* 2004), section 6. (These will be referred to as 'group A'.)
- (3) Employees of AWE or those directly involved in minor trials at Maralinga ('group B').
- (4) Groups A and B plus other men with a recorded non-zero film badge dose.
- (5) All those not falling in one of the preceding groups.
- (6) All test participants.

Among participants present at a major operation, mortality for leukaemia and multiple myeloma was not significantly different from national rates and mortality from all solid cancers combined was significantly lower than national rates. Furthermore, mortality rates of these diseases were consistent with those amongst the controls, with the exception of leukaemia, where there was some indication of raised risks, particularly over the period 2–25 years since first test participation.

Generally, similar findings arose both for the groups identified by MOD as liable to exposure to radiation ('group A'), and for participants employed by AWE or directly involved in the minor trials at Maralinga ('group B'). However, the numbers of myelomas and leukaemias in both these groups were small and hence the statistical uncertainties were large. Mortality from all cancers other than leukaemia and myeloma was significantly lower than national rates in both groups A and B. However, rates in group A were significantly less than those in the controls (RR 0.71, 90% CI 0.55–0.92), whereas rates in group B were significantly greater than those among the controls (RR 1.31, 90% CI 1.03–1.66).

For the fourth grouping in table 7, men in groups A and B plus those who were recorded as having a radiation dose, mortality from leukaemia and myeloma was consistent with national rates. The estimated relative risks compared with controls were greater than one but not significantly so. Mortality from all other cancers was significantly less than national rates and similar to that among the controls.

For participants not in any of the preceding groups, mortality from myeloma and all cancers other than leukaemia and myeloma was consistent with national rates and with the corresponding rates among controls. However, leukaemia rates in this group of 'other test participants' tended to be raised relative both to national rates and to those for controls. This was particularly marked during the period 2–25 years after first test participation (SMR 221; RR 7.63, 90% CI 2.73–21.8).

As noted in section 4.2, separate analyses were carried out for a group of 1520 men with no more potential for exposure to radiation than the general population (Muirhead *et al* 2003b). Findings from analyses of mortality are summarised in table 10. The SMRs for all causes of death, all neoplasms taken together, other diseases and accidents and violence were very similar to those in the main group of test participants. For none of these endpoints was the risk relative to controls significantly different from one. For leukaemia excluding CLL the SMR was 112, not significantly different from 100 and the relative risk (2.23) was not significantly different from one. Similar findings arose for leukaemia excluding CLL over the period 2–25 years following first test participation. Furthermore, the SMRs and relative risks for leukaemia excluding CLL shown in table 10 are similar to the corresponding values for the main cohort

given in table 3, so indicating that the exclusion of this group of men from the main cohort of test participants has not affected inferences. Among other types of cancer, both the SMR and the relative risk for stomach cancer were significantly elevated. However, Muirhead *et al* (2003b) examined mortality for 27 distinct types of cancer, and it is not surprising that findings significant at the 1 in 20 level would be found for one type of cancer. We note that both the SMR (196, based on three deaths) and relative risk (2.69) were also elevated for liver cancer, though neither increase was statistically significant. As with the main analysis, there was less evidence of an excess for primary liver cancer, although the very small numbers restrict inferences.

5.4.6. Comparisons of participants in tests in Australia and in the Pacific. Many test veterans have a specific interest in either the Pacific tests or those in Australia. Accordingly, in addition to the analyses described in the published papers we have also undertaken a comparison of participants in the Australian tests with those in the Pacific tests using the same database as for the published third analysis. The first analysis included such a comparison for leukaemia excluding chronic lymphatic leukaemia and multiple myeloma (Darby *et al* 1988b). Results of the latest analysis are shown in table 8. For the categories of all causes of death and of all neoplasms other than leukaemia and multiple myeloma, SMRs for both groups of participants were significantly below those in the general population. For all neoplasms other than leukaemia and multiple myeloma, the relative risk for participants in Pacific tests relative to those in Australia was below one, though the difference did not quite reach statistical significance (RR = 0.90; 90% CI 0.80–1.00, one-sided $p = 0.056$, two-sided $p = 0.11$).

For multiple myeloma and for leukaemia (whether including CLL or not), the numbers of deaths amongst both groups of participants were small. SMRs were not significantly different from 100 and there was no statistically significant difference in mortality between those at Australian tests and those at tests in the Pacific.

The investigators do not regard these results as giving strong evidence for a difference in cancer mortality between those taking part in tests in Australia and those in the Pacific, as had been suggested by Baverstock (2003); see also Muirhead and Kendall (2003).

Results for individual operations are given in appendix E of the published report (Muirhead *et al* 2003b). These figures contain a typographical error. For operation Mosaic, Muirhead *et al* 2003b reported no cases of leukaemia or of leukaemia excluding CLL for the whole of the follow-up period. In both instances, the correct figure was 3. The expected numbers were 3.2 and 2.6 respectively and the SMRs are therefore close to one. The tables in appendix E of the report refer to men who were present at specified operations. If a man was at two or more operations, he will appear in more than one table. Men who attended tests in both the Pacific and Australia are included in both SMR analyses in table 8 of the present review but are excluded from the relative risk calculation.

The data presented in table 8 also include men who went to test locations but were not present at the time of a detonation. Analyses based solely on men present at a major operation, or taking part in the Maralinga Experimental Programme, give generally similar results. For leukaemia excluding CLL, there was slightly more suggestion of a higher mortality rate among those present at Pacific tests relative to those present at Australian tests, but the evidence was weak. For the full follow-up period the relative risk was 2.01, with 90% confidence interval 0.86–4.86 (one-sided $p = 0.09$, two-sided $p = 0.14$). Over the period 2–25 years after first test involvement, where numbers of cases are lower, the relative risk was 5.5, with 90% confidence interval 0.76–98 (one-sided $p = 0.09$, two-sided $p = 0.14$). Furthermore, the SMR for leukaemia excluding CLL during the 2–25 year period among men present at Australian tests was not significantly reduced ($p = 0.14$). These p -values differ from those presented by Baverstock (2003), which were based on an approximate analysis.

5.4.7. Mortality in independent responders. As described in sections 4.3 and 5.2 of the companion review article (Kendall *et al* 2004), a number of test participants were made known to the investigators independently of the Ministry of Defence. These independent responders were divided into those who had already come to light during searches of contemporary records and those whose test participation was confirmed only after their details had been given to the investigators. Death rates of these two groups were generally similar (results not shown here; see table 7.14 of Darby *et al* (1988b)). This provides reassurance that the cohort identified through MoD records did not have markedly different mortality from other test participants. In both groups mortality rates—particularly for all causes combined and for all cancers combined—were very high relative to national rates in the period during which the individuals were notified to the researchers (table 9). This period extended up to 28 February 1993, when enrolment for the second analysis ceased. During the subsequent period, mortality rates were generally closer to national values. This is consistent with a strong selection effect operating at the time at which these men were made known to the investigators.

5.5. Conclusions drawn from the third analysis

Taking into account the results of the epidemiological analyses described above and also the other sources of information the investigators concluded that:

Overall levels of mortality and cancer incidence in UK nuclear weapons test participants continued to be similar to those in a matched control group, and overall mortality has remained lower than expected from national rates. There was no evidence of an increased risk of multiple myeloma among test participants in recent years, and the suggestion in the first analysis of this cohort of a raised myeloma risk relative to controls is likely to have been a chance finding. There was some evidence of a raised risk of leukaemia other than chronic lymphatic leukaemia among test participants relative to controls, particularly in the early years after the tests, although a small risk may have persisted more recently. This could be a chance finding, in view of low rates among the controls and the generally small radiation doses recorded for test participants. However, the possibility that test participation caused a small absolute risk of leukaemia other than chronic lymphatic leukaemia cannot be ruled out.

6. Summary

Concerns about the health of participants in nuclear weapons tests go back three decades. These concerns have tended to centre on malignant disease, probably because of its known link with radiation. The UK has national registers of mortality and cancer incidence data and is well placed to study these endpoints. It is less easy to examine suggestions of, for example, congenital abnormalities in offspring. However, evidence from, for example, the survivors of the atomic bombs on Hiroshima and Nagasaki suggests that malignant disease may be the most readily observed consequence of radiation exposure.

Three epidemiological analyses of mortality and cancer incidence in UK participants in the UK atmospheric weapons testing programme have been published over a 15 year period. A consistent finding has been the so-called ‘healthy soldier effect’, that mortality from broad causes of death is generally below that in the general population, but similar to that in a matched series of controls.

The first analysis produced a striking excess of leukaemia (excluding chronic lymphatic leukaemia) and of multiple myeloma in test participants relative to controls. However, this

seemed to be more a consequence of low levels in the controls rather than of elevated levels in test participants.

The second and third analyses have provided no convincing evidence of excess multiple myeloma amongst test participants. This increases the likelihood that chance was responsible for the difference seen in the first analysis between the rates of multiple myeloma in test participants and the controls. In the case of leukaemia, however, there is some evidence for a persistent risk. This suggestion receives some support from studies of participants in other nuclear tests, particularly in the United States. There is little evidence that radiation, rather than some other factor connected with test participation, could be the cause of any possible excess.

Since the study cohort includes only about 85% of men meeting the definition of test participation it is important to consider the question of whether it is typical of test veterans as a whole, that is, whether mortality and cancer incidence in the study cohort might have been different in the 15% who were not included. The investigators were very alert to this risk when the cohort was being assembled and indications were that any bias was small (Darby *et al* 1988b). Furthermore, most of the deaths and cancers in later analyses occurred after the cohort was identified nearly 20 years ago. It is implausible that any hypothetical selection effect should manifest itself to any material extent—if at all—in these subsequent years.

If the recorded radiation exposures of participants in the UK atmospheric tests were correct, the collective dose to participants was about 17 man Sieverts. If the established radiation risk factors (NRPB 1993) apply, then this implies that about one radiation induced cancer would be expected in the whole group of test participants. There would be no chance of detecting this against the rather high natural death rate (the data of table 3 indicate that about 1660 cancer deaths would be expected in the period up to 1998 if national death rates applied). However, if radiation exposures were much larger, or if participants were exposed to some other risk factor, then a detectable effect might arise.

The published studies also analysed separately special groups who might have been at higher risk from their role in the tests. These groups included those for whom there was a record of exposure to radiation. No striking findings were observed, though the numbers of individuals in some groups were small and hence the statistical uncertainties for rare diseases like leukaemia and multiple myeloma were large.

The three published studies have been conducted with possible consequences of exposure to radiation primarily in mind. But they would also have detected any substantial mortality and cancer incidence induced by other agents.

In view of the continuing public interest in the health of participants in nuclear weapons tests, it is proposed that further periodic analyses of the cohort should be undertaken.

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Appendix. Methods of analysis

The analysis has two main components.

- Comparisons of mortality in test participants and in controls with national rates by means of standardised mortality ratios (SMRs). An SMR of 100 for a particular group of men

indicates that mortality rates in that group were the same as mortality rates of men of the same ages in the general population during the same time-period. An SMR of 150 indicates that the age-specific mortality rates in the group are about 50% higher than in the general population, while an SMR of 50 indicates that the age-specific mortality rates are about 50% lower.

- Direct comparisons of mortality and cancer incidence in participants and controls using relative risks (RRs). A relative risk of 1.00 indicates that the age-specific mortality (or cancer incidence) rates in the two groups during the period under study are the same, while an RR of 1.50 (or 0.50) would indicate that the rates in the test participants are 50% higher (or lower) than in the control group.

Cancer incidence was assessed in this study using both registration and mortality data. Since registration data are not complete in the most recent years, the cancer incidence rates ascertained in this study have not been compared with national cancer registration rates. However, because the same approach was used to ascertain cancer incidence among test participants and controls, direct comparison of these two groups was possible.

Both for SMRs and RRs, the analysis uses numbers of person-years, i.e. the length of time that each man was in the study, summed over the men included in the study.

In the SMR analysis, the expected numbers of deaths in each age and calendar year group were calculated by multiplying the person-years in each group by the corresponding mortality rates for men in England and Wales, and summing the resulting values. Standardised mortality ratios (SMRs) were then calculated as the ratio of the total number of observed to the total number of expected deaths, multiplied by 100.

The relative risk in participants compared to controls will usually be close to the ratio of the SMRs in the two groups. But this is not exactly the case because a more detailed methodology is used for the relative risk analysis. In calculating SMRs, person years are subdivided only by age and calendar year (both in 5 year groups). In the calculation of relative risks they are also subdivided by service or employer (i.e. RN, Army, RAF, AWE) and by rank (officers or other ranks). Furthermore, national rates are not used in the calculation of relative risks because participants and controls are compared directly.

An SMR of 100 means that the overall level of mortality is the same as in the general population. A relative risk of one means that mortality or cancer incidence in test participants is the same as in controls. But it would not be expected that, in the absence of any real difference between the two groups, all the SMRs would be exactly 100 and all the relative risks exactly one. In the same way, tossing a coin six times will not always give three heads and three tails. Some way is needed to decide how much weight should be given to what may appear to be unusual values.

The probability or *p*-value gives the chance that a result as extreme as or more extreme than that observed would arise as a result of random variations. The smaller the *p*-value, the less likely it is that chance is responsible for the finding. Very often a *p*-value of 0.05 is used as the dividing line between findings which are said to be statistically significant and those that are not. A lower value, however, cannot be taken to imply that the findings are not due to chance, only that the probability that chance would produce such an effect was less than 1 in 20. When *p*-values for many causes of death or cancers have been calculated, as in the present study, it is to be expected that some *p*-values lower than 0.05 will arise simply due to the play of chance. This is discussed below.

The confidence interval is another concept related to the *p* value. If a 95% confidence interval for a relative risk is given as say 1.1–2.0 then there is a 95% chance that the true value of the relative risk falls within this range and only a 5% chance that the true value lies either

below or above the interval. In this particular example, the fact that the lower bound of the confidence interval is above one is an indication that the relative risk is elevated to a statistically significant degree, but not necessarily that some special risk must have been present.

But another question needs to be considered in interpreting statistical results. Is there a reason to expect that, say, relative risks will be increased rather than decreased? For example, the balance of the evidence is that radiation increases cancer rates rather than decreasing them. So there is an *a priori* reason to be interested in increased relative risks in an exposed group compared to the unexposed.

When there is an *a priori* reason to be interested in increases rather than decreases in risk, then researchers may choose to use 'one-sided tests', i.e. a test in one direction only, and a 90% confidence interval. On the other hand, if equal weight is to be given to both increases and decreases in risk, then a 'two-sided test' (i.e. a test in both directions) and a 95% confidence interval may be used. In both instances a result will be said to have reached the conventional ($p < 0.05$) level of statistical significance if the probability is 1 in 20 or less that a result at least as extreme as that observed arose in the absence of an underlying effect. In the case of a one-sided test for, say, an increase in relative risk, attention is focused on the upper 5% of the distribution and no attention is paid to results in the lower tail. In the case of a two-sided test, a result would be described as significant if it fell above the upper 2.5 percentile or below the lower 2.5 percentile of the distribution. Thus a result which was described as significant if a one-sided test was applied might not achieve significance under a two-sided test. There may be cases where it is difficult to decide which is more appropriate. However, it is important that researchers make it clear which test has been chosen and that those evaluating the study bear this question in mind.

In the test veterans analyses, two-sided tests and 95% confidence intervals were used to assess whether the SMRs differed to a statistically significant extent from 100 since both increases and decreases relative to national rates were of interest. In the first and second analyses, one-sided tests were carried out for relative risks, but the third analysis included both one- and two-sided tests.

References

- ACHRE (Advisory Committee on Human Radiation Experiments) 1995 *Final Report* (Washington, DC: US Government)
- Australian Department of Veterans Affairs 2003 http://www.dva.gov.au/adf/health_studies/mainhs.htm#apbntp
- Baverstock K 2003 The 2003 NRPB report on nuclear-test veterans *Lancet* **361** 1759–60
- Cartwright R A, Alexander F E, McKinney P A and Ricketts T J 1990 *Leukaemia and Lymphoma: An Atlas of Distribution within Areas of England and Wales 1984–1988* (London: Leukaemia Research Fund)
- Cologne J B, Tokuoka S, Beebe G W, Fukuhara T and Mabuchi K 1999 Effects of radiation on incidence of primary liver cancer among atomic bomb survivors *Radiat. Res.* **152** 364–73
- Commonwealth Department of Health 1983 *Health of Atomic Test Personnel* (Canberra: Australian Government Publishing Service)
- Cuzick J and De Stavola B 1988 Multiple myeloma—a case-control study *Br. J. Cancer* **57** 516–20
- Darby S C, Doll R, Gill S K and Smith P G 1987 Long term mortality after a single treatment course with x-rays in patients treated for ankylosing spondylitis *Br. J. Cancer* **55** 179–90
- Darby S C, Muirhead C R, Doll R, Kendall G M and Thakrar B 1990 Mortality among United Kingdom servicemen who served abroad in the 1950s and 1960s *Br. J. Ind. Med.* **47** 793–804
- Darby S C *et al* 1988a A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes *Br. Med. J.* **296** 332–8
- Darby S C *et al* 1988b Mortality and cancer incidence in UK participants in UK atmospheric nuclear weapon tests and experimental programmes *NRPB-R214* (Chilton: NRPB) (London: HMSO)
- Darby S C *et al* 1993a Further follow-up of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes *Br. Med. J.* **307** 1530–5

- Darby S C *et al* 1993b Mortality and cancer incidence 1952–1990 in UK participants in the UK atmospheric nuclear weapon tests and experimental programmes *NRPB-R266* (Chilton: NRPB) (London: HMSO)
- DTRA 2003 Radiation exposure in US atmospheric nuclear weapons testing *Nuclear Test Personnel Review Programme* Defence Threat Reduction Agency Web Site http://www.dtra.mil/news/fact/nw_ntprpre.html
- Hansard 1999 *Mr Spellar on Multiple Myeloma* (Feb. 1999) col 412
- Hansard 2000 *Dr Moonie on Nuclear Test Veterans* (Feb. 2000) col 34W
- Institute of Medicine 1996 *Mortality of Veteran Participants in the CROSSROADS Nuclear Test* (Washington, DC: National Academy Press)
- Institute of Medicine 2000 *The Five Series Study: Mortality of Military Participants in US Nuclear Weapons Tests* (Washington, DC: National Academy Press)
- Johnson J C, Thaul S, Page W F and Crawford H 1996 *Mortality of Veteran Participants in the CROSSROADS Nuclear Test* (Washington, DC: National Academy Press)
- Kendall G M, Muirhead C R, Darby S C, Doll R, Arnold L and O'Hagan J A 2004 Epidemiological studies of UK test veterans: I. General description *J. Radiol. Prot.* **24** 199–217
- Muirhead C R, Goodill A A, Haylock R G E, Vokes J, Little M P, Jackson D A, O'Hagan J A, Thomas J A, Kendall G M and Silk T J 1999 Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers *J. Radiol. Prot.* **19** 3–26
- Muirhead C R and Kendall G M 2003 UK nuclear test-veterans *Lancet* **362** 331–2
- Muirhead C R *et al* 2003a Follow up of mortality and incidence of cancer 1952–98 in men from the UK who participated in the UK's atmospheric nuclear weapons tests and experimental programmes *Occup. Environ. Med.* **60** 165–72
- Muirhead C R *et al* 2003b Mortality and cancer incidence 1952–1998 in UK participants in the UK atmospheric nuclear weapons tests and experimental programmes *NRPB-W27* (Chilton: NRPB)
- NRPB (National Radiological Protection Board) 1993 Estimates of late radiation risks to the UK population *Docs NRPB 4(4)* (Chilton: NRPB)
- NRPB (National Radiological Protection Board) 2003 Risk of leukaemia and related malignancies following radiation exposure: estimates for the UK population *Docs NRPB 14(1)* (Chilton: NRPB)
- Parliament 1983 *The Naval, Military and Air Forces etc (Disablement and Death) Service Pensions Order 1983, Statutory Instrument* 1983/883
- Pearce N, Prior I, Methven D, Culling C, Marshall S, Auld J, de Boer G and Bethwaite P 1990 Follow-up of New Zealand participants in British atmospheric nuclear weapons tests in the Pacific *Br. Med. J.* **300** 1161–6
- Pearce N, Winkelmann R, Kennedy J, Lewis S, Purdie G, Slater T, Prior I and Fraser J 1997 Further follow-up of New Zealand participants in United Kingdom atmospheric nuclear weapons tests in the Pacific *Cancer Causes Control* **8** 139–45
- Preston D L *et al* 1994 Cancer incidence in atomic bomb survivors. Part III: Leukemia, lymphoma and multiple myeloma, 1950–1987 *Radiat. Res.* **137** S68–97
- Rabbitt Roff S 1999a A long time coming *New Sci.* (6 February)
- Rabbitt Roff S 1999b Mortality and morbidity of members of the British Nuclear Tests Veterans Association and the New Zealand Nuclear Tests Veterans Association and their families *Med. Confl. Surviv.* **15** (Suppl. 1)
- Thomas D 1998 Study of UK men who had participated in the UK nuclear weapons test programme *J. Radiol. Prot.* **18** 209–10
- UNSCEAR (United National Scientific Committee on the Effects of Atomic Radiation) 2000 *Sources and Effects of Ionizing Radiation (Report to the General Assembly, with Scientific Annexes)* (New York: United Nations)
- Watanabe K K, Hang H K and Dalager N A 1995 Cancer mortality risk among military participants of a 1958 atmospheric nuclear weapons test *Am. J. Public Health* **85** 523–7
- Weiss H A, Darby S C, Fearn T and Doll R 1995 Leukemia mortality after x-ray treatment for ankylosing spondylitis *Radiat. Res.* **142** 1–11