Mortality and cancer incidence 1952–2017 in United Kingdom participants in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes

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PAPER

Mortality and cancer incidence 1952–2017 in United Kingdom participants in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes

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Abstract

This study examines the mortality and cancer incidence experience among men who took part in the United Kingdom's atmospheric nuclear weapon tests between 1952–67. A cohort of 21 357 servicemen and male civilians from the UK who participated in the tests and a group of 22 312 controls were followed between 1952 and 2017. Analyses of mortality and cancer incidence were conducted. The overall mortality rate in the test participants was slightly higher relative risk (RR = 1.02, 90% CI 1.00–1.05, $p = 0.04$) than that in the control group. This difference was driven by similar increased risks for both all cancers combined (RR 1.03, 90% CI 1.00–1.07) and all non-cancer diseases (RR = 1.02, 90% CI 1.00–1.05). Leukaemia excluding chronic lymphatic incidence showed evidence of being raised relative to controls (RR = 1.38, 90% CI 1.10–1.75, $p = 0.01$). Leukaemia risks were driven by increased risks for chronic myeloid leukaemia (CML) (RR = 2.43, 90% CI 1.43–4.13, $p = 0.003$). Among non-cancer outcomes only cerebrovascular diseases showed increases in participants relative to controls. UK nuclear weapon tests participants have lower mortality rates compared to the national population although rates are slightly (2%) higher than in the study control group. Variation in background characteristics, that could not be accounted for in the analysis (e.g. smoking habits, diet), are a possible explanation for this difference. For leukaemia evidence of increased risk in the early years after the test has generally continued to diminish with time although for CML risks have persisted. There was some evidence that participants had higher mortality rates from cerebrovascular diseases than those in the control group. Assuming recorded radiation exposures (generally very low) are a true reflection of actual exposures then it is unlikely that any observed health effect will have been caused by radiation exposure.

1. Introduction

The UK conducted a series of 21 atmospheric nuclear weapon tests in Australia and at islands in the Pacific Ocean between 1952 and 1958. Further experiments relating to the nuclear weapons programme where radioactive materials were also dispersed into the atmosphere were carried out at Maralinga and Emu Field in Southern Australia between 1953 and 1963 and survey and clean-up operations continued until 1967. In addition, UK personnel based at Christmas Island also participated in US nuclear weapon tests between 1962 and 1964.

Over the last 40 years, media reports highlighting concern among veterans' organisations that participants in the UK nuclear weapon tests may have suffered ill-health because of their involvement have persisted. The first of these reports appeared in the early 1980s when the number of cancer deaths in a group of self-identified participants in the nuclear test programme were reported [1, 2]. However, at that time, it was unclear how many deaths would have been expected in these men. In response to these concerns, in 1983 the Ministry of Defence (MOD) commissioned the National Radiological Protection Board (NRPB) to study

the health of the participants. From MOD archives, a study population of over 20 000 men was identified as having participated in the test programme and a similar-sized control group was selected from the same archives. The Nuclear Weapons Test Participants Study (NWTPS) is now maintained by the UK Health Security Agency. The cohort has been described in detail previously [3].

Three analyses of mortality and cancer incidence have been undertaken to date: the first based on follow-up to the end of 1983 [4, 5], the second based on follow-up to the end of 1990 [6, 7] and the third based on follow-up to the end of 1998 [3, 8–10]. None of these analyses provided evidence that test participation had had a detectable effect on overall life expectancy or on the total risk of cancer incidence. The first analysis did, however, find that for leukaemia and multiple myeloma, both the mortality rate and the rate of incident cancers were higher among the test participants than among the controls [4, 5], but the finding of increased risk of multiple myeloma was not supported by the results of second [6, 7] or third analysis [8, 9]. This pattern suggests that the earlier excess of this disease was a chance finding. Both the second and third analyses continued to show some evidence of a raised risk of leukaemia other than chronic lymphatic leukaemia (CLL) among test participants, compared to that seen in the controls, especially in the years directly following the tests, but a small risk may have persisted more recently. Although these earlier results may be chance findings, the third analysis concluded that the possibility that test participation may have caused a small increased risk of leukaemia could not be completely ruled out.

Since the third analysis of the NWTPS cohort, health concerns among some participants have persisted. During this time an additional 19 years of follow-up information has now been accrued making it possible to study, in more detail and with greater statistical certainty, the potential lifelong health impact of test participation. This paper reports on the findings of a fourth analysis of this cohort.

2. Material and methods

2.1. Study population

The population is essentially the same as that in the third analysis [8, 9]. Contemporary records held by the MOD were searched to identify test participants among servicemen and civilian employees of the Atomic Weapons Establishment (AWE) and Atomic Energy Research Establishment. These men had visited at least one of the test locations (Monte Bello Islands, Emu Field and Maralinga Range in Australia; Malden and Christmas Islands in the Pacific Ocean) at the relevant times or had sampled radioactive plumes from the explosions. The analysis is based on 21 357 test participants, of whom 6305 (29%) were in the Royal Navy, 5794 (27%) were in the army, 8443 (40%) were in the Royal Air Force and 815 (4%) were civilians [9]. The cohort was assembled from the extensive searches of MOD archival records (described in the first analysis report [5]), but no complete listing of test participants was available. Since it could not be assumed that all participants had been identified, the cohort was checked for completeness. Information was sought from other sources, such as veterans' organisations, and the overlap between the men identified from the MOD and non-MOD sources was evaluated. Based on this information the main cohort of participants studied in this analysis was estimated to be 85% complete which is unchanged from the last analysis (further details are provided in the supplementary material available online at stacks.iop.org/JRP/42/021507/mmedia).

A control group of 22 312 men who did not participate in the tests was also identified from MOD archives. This number is slightly fewer than reported in the third analysis because 21 controls were identified as actually being lost to follow-up (either emigrated or untraced) prior to their defined start of follow-up date. For test participants who had been servicemen, controls were selected from among other servicemen who served in tropical or subtropical areas at the time of the tests. For civilian test participants, controls were chosen from other men employed by AWE at the time of the tests. Controls were matched with participants for age, type of armed service, rank (officers and other ranks; broad socioeconomic class for civilians) and date of entry to the study. The test participants and controls had very similar distributions by service and rank (see supplementary table S1), as well as by year of birth, year of enlistment or employment and year of discharge or end of employment [7, 9]. Great care was taken to ensure participants and controls were enrolled based on objective criteria and without reference to their health status. Further details on the selection of both the participant and control groups can be found in the first and third analysis reports [3, 5, 9].

2.2. Radiation exposure information

Most of the information on radiation exposures to test participants comes from records of radiation dosimeters (film badges) issued to some of the participants. The general policy during the early tests in Australia was to monitor almost all the participants for radiation exposure. However, by the time of the later Pacific tests, this policy had been revised and, if it was judged based on the previous tests that measurable exposure was unlikely to occur, then monitoring was not carried out. Dose monitoring records were available for 23% of the participants, of whom 64% had zero recorded dose (see supplementary table S2). Only 8% of

the total participant cohort had non-zero recorded radiation doses and the mean dose from gamma radiation amongst these men was 9.9 mSv. In addition to veterans with dosimetry information, the MOD also identified participants with the greatest potential for exposure based on the duties that they performed. These participants are categorised throughout the article and in the supplementary tables as either Groups A, 759 workers identified as most likely to have received significant radiation doses, or Group B, 1041 participants identified as most likely to have received any undocumented inhalation or ingestion of radionuclides. Further details on the definition of these groups is given in the supplementary information and in previous reports [3, 9].

2.3. Follow-up

Work was undertaken to determine the vital status of all test participants and controls on 31 December 2017 and to identify as many as possible of those who had emigrated by that time. The methods employed were similar to those adopted in the previous three [5, 7, 9] analyses with information collected on both mortality and incident cancers. As of 31 December 2017, 9% of test participants and 8% of controls had emigrated (1998 and 1902 respectively), 56% of both groups had died (11 906 participants and 12 549 controls), 34% of participants (7301) and 35% of controls (7718) were alive and living in the UK, and less than 1% of both groups were lost to follow up (152 and 143 respectively). Causes of death were coded according to the ninth revision of the International Classification of Diseases (ICD-9) up to 2000 [11] and to the tenth revision (ICD-10) [12] thereafter. For incident cancers, events were coded to ICD-9 up to 1994 and to ICD-10 from 1995.

2.4. Method of analysis

The methods of analysis were very similar to those used previously [5, 7, 9]. Test participants were entered into the study on the date of their first test involvement. For controls, the date of entry to study was calculated differently according to service and rank. Controls in the Royal Navy were selected from ships' ledgers and entered the study on the last day of the ledger period from which they were selected. RAF officer and airman controls entered the study six months and two months respectively after starting tropical service overseas as this was the minimum length of overseas service required in these groups. Army officer controls were selected from lists of Army officers in tropical postings on dates around the time of the tests. These controls entered the study one year after the start of their overseas service as this date was the only information available for these officers whose typical length of overseas service was two years. Soldier controls were selected from discharge collations meaning that they were alive at the termination of their reserve liability, so they entered the study at this date. Civilian controls entered the study on the date of the first test involvement of the participant for whom they were matched. Full details on the methods used for the selection of the control group can be found in the first analysis report [5].

For the analysis of mortality, men were regarded as being at risk until their date of death, emigration, or 31 December 2017, whichever came earliest. For the analysis of cancer incidence, men were regarded as being at risk until their date of cancer registration, death, emigration, or 31 December 2016 (due to incomplete incidence information in 2017), whichever came earliest. For the small number of untraced men follow-up was truncated at the date of discharge from the services or end of employment (for untraced civilians) in both mortality and incidence analyses.

There were two main parts to the analysis. In the first, the numbers of deaths or incident cancers in each of the participant and control groups were compared to the expected numbers in these groups based on the observed national mortality and cancer incidence statistics. For mortality, the analysis covered the whole period under study (i.e. from the first tests in 1952), while for cancer incidence this comparison was restricted to 1971 onwards as reasonable coverage of national cancer incidence data was not available until that date. The results of this analysis are presented as standardised mortality ratios (SMRs) or standardised incidence ratios (SIRs). While comparison of participants rates to a national reference population can be useful for detecting any large effects associated with the tests, there are known difficulties in comparing two populations with different background characteristics which can bias results [13, 14]. In the second part of the analysis, mortality and cancer incidence rates were compared directly between participants and controls and the results of this analysis are described using the relative risk (RR) measure. As the control group was specifically selected to have similar background characteristics to the participants (e.g. employer/service, rank/socioeconomic status, calendar period of service, area of service and age), the comparison is less prone to bias. Therefore, more emphasis has been placed on RR results in determining any potential detrimental effect associated with the tests than results from the SMR or SIR analysis.

To derive the SMRs and SIRs the person-years were subdivided, as appropriate, by Service or employer, rank, five year age group and calendar period. Expected numbers of deaths/cases in each group were calculated by multiplying the person-years in each age and calendar year group by the corresponding specific

mortality/incidence rates for men in England and Wales and summing the resulting values. SMRs and SIRs were then calculated as the ratio of the observed to the expected number of deaths/cases, multiplied by 100. Tests for linear trends in SMRs by time since first test participation were based on Poisson regression [15].

To derive the RRs to compare both mortality and cancer incidence rates among the test participants directly with those in the control group, the deaths/cases and person-years were subdivided by age (in five year groups), calendar period (in five year groups), Service or employer (i.e. RN, Army, RAF, AWE) and either by rank (officers or other ranks) for those in the Services or by social class (class 1 or other classes) for AWE employees. The RRs were then estimated by the method of maximum likelihood [15] using Poisson regression which estimates the RR having adjusted for each of the factors mentioned above. For the RR parameter estimates, hypothesis tests and confidence intervals were based on the likelihood ratio statistic and direct evaluation of the profile likelihood. As in all previous reports on this study [5, 7, 9], the primary interest was in evaluating any potential increase in risk among test participation relative to the matched control group. Therefore, we have again reported one-sided p-values and corresponding 90% confidence intervals for the RR parameter estimates. These results may be interpreted as one-sided tests at the 5% level of statistical significance. All other statistical tests and associated p-values are based on two-sided tests.

For the purposes of this article, much of the analysis was restricted to selected subsets of cancer, non-cancer and leukaemia sub-groups identified to be of prior interest in this cohort [5, 7, 9]. In the case of leukaemia, results are presented for all leukaemias combined, all leukaemia excluding chronic lymphatic leukaemia (non-CLL) and for the four main subtypes of leukaemia: Acute lymphoblastic leukaemia (ALL), chronic lymphocytic leukaemia (CLL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML). Due to small numbers, supplementary analysis on subsets of the participant cohort focuses on all leukaemia combined and 'non-CLL' leukaemia because of prior evidence that CLL is not related to radiation exposure. See supplementary tables S3–S5 for full definitions of the disease groups under study. While the main analysis focuses on disease groups identified to be of prior interest, some supplementary analyses were also conducted on an expanded set of both cancer and non-cancer diseases groups. Definition of these groups and the results of this analysis are presented in the supplementary material (tables S20(a) and (b)).

Throughout the main text the results presented are generally based on the whole participant cohort and control group. A number of sub-group analyses were also undertaken, some of which are discussed in the 'Mortality and cancer incidence in test participants by type and degree of exposure' section of the results with tabular results presented in the supplementary material. These include the analysis of participants with individual radiation monitoring records, which, as well as including an examination of SMR/SIR/RR results also includes tests for trend in recorded gamma dose based on the score statistic [15]. Also included are sub-group analyses of participants included in special exposure Groups A and B (both defined above). Results from analyses of participants only involved in major operations and those involved in tests in the Pacific and Australia have also been given separately.

3 Results

3.1. All causes mortality

Table 1 shows that for all causes of mortality, there was strong evidence that rates in both participants and controls were lower than those in men of the same ages in England and Wales (SMRs of 90 and 88 respectively, $p < 0.001$) over the whole follow-up period. Comparing participants with controls, the RR for all causes of death showed some evidence of a small difference in mortality between the two groups (RR = 1.02, 90% CI 1.00–1.05, $p = 0.04$). There was strong evidence that rates among both participants and controls were lower than national rates in the period used in the previous analysis (i.e. up to the end of 1998) and this remained the case during the period 1999–2017 with rates between 9 and 13% lower than national levels (table 2). Whilst the overall mortality rate among participants for all causes combined was consistent with the corresponding rate among controls up to the end of 1998 (RR = 1.01, 90% CI 0.98–1.05), there was some evidence of a raised overall mortality rate among participants in the more recent period of follow-up (RR = 1.03, 90% CI 1.00–1.05, $p = 0.04$).

3.2. Cancer mortality excluding leukaemia

Over the whole follow up period, slightly fewer deaths were observed for all cancers combined than expected based on national rates (SMRs were 97 for test participants and 94 for controls). For all cancers combined, the RR was raised to a similar extent (3%) as for all causes of death but the difference failed to reach statistical significance (RR = 1.03, 90% CI 1.00–1.07, $p = 0.07$), possibly due to the smaller number of cancer deaths (4038 cancer deaths compared to 11 906 deaths in total). Mortality among test participants or controls was lower than national rates for several cancer types: stomach, amongst the participants; all cancers, stomach, lung, prostate and bladder cancers among the controls. The only cancers that showed evidence of excesses

Table 1. Observed numbers of deaths and SMRs among test participants and controls, with RRs of mortality among test participants compared with controls, for selected causes of death over the whole follow-up period.

	Participants			Controls			Mortality rates in test participants relative to controls	
Cause of death	Obs	SMR	*p*-val	Obs	SMR	*p*-val	RR (90% CI)	*p*-val
All causes	11 906	90 ***	<.001	12 549	88 ***	<.001	1.02* (1.00, 1.05)	0.035
All neoplasms	4118	97 *	0.048	4303	94 ***	<.001	1.03 (0.99, 1.07)	0.081
All cancers	4038	97	0.076	4213	94 ***	<.001	1.03 (1.00, 1.07)	0.075
Benign and unspecified	63	80	0.072	78	91	0.465	0.88 (0.66, 1.16)	0.782
Buccal cavity and pharynx	74	116	0.224	94	138 **	0.003	0.86 (0.66, 1.11)	0.839
Mouth and pharynx	56	133 *	0.046	66	147 **	0.004	0.92 (0.68, 1.24)	0.686
Stomach	182	82 **	0.005	165	68 ***	<.001	1.20* (1.00, 1.43)	0.049
Liver and gallbladder	103	97	0.775	114	100	0.967	0.96 (0.77, 1.21)	0.606
Liver	95	104	0.764	99	101	0.966	1.03 (0.81, 1.30)	0.430
Respiratory system	1285	100	0.999	1305	94 *	0.041	1.07* (1.00, 1.14)	0.049
Lung	1138	97	0.373	1163	93 **	0.008	1.06 (0.99, 1.13)	0.089
Pleural cancer	96	129 *	0.020	90	113	0.274	1.19 (0.93, 1.51)	0.121
Melanoma	60	127	0.086	63	125	0.094	1.04 (0.77, 1.40)	0.410
Non-melanoma skin cancer	17	113	0.687	12	73	0.336	1.59 (0.85, 2.97)	0.110
Prostate	444	102	0.624	418	89 *	0.012	1.16* (1.03, 1.30)	0.017
Bladder	154	93	0.397	145	81 **	0.009	1.17 (0.96, 1.41)	0.093
Kidney and ureter	107	99	0.976	144	125 *	0.012	0.80 (0.65, 0.99)	0.960
Brain and CNS	116	102	0.847	123	102	0.811	0.99 (0.80, 1.22)	0.546
Multiple myeloma	61	85	0.237	71	93	0.558	0.93 (0.70, 1.24)	0.661
Leukaemia	114	93	0.446	104	79 *	0.016	1.14 (0.91, 1.43)	0.162
Leukaemia excluding CLL	96	102	0.860	79	79 *	0.035	1.26 (0.98, 1.62)	0.065
Acute lymphatic (ALL)	9	136	0.444	5	72	0.623	1.73 (0.68, 4.43)	0.168
Chronic lymphatic (CLL)	18	62 *	0.036	25	79	0.274	0.78 (0.47, 1.29)	0.794
Acute myeloid (AML)	65	105	0.713	60	91	0.528	1.13 (0.84, 1.52)	0.249
Chronic myeloid (CML)	18	113	0.661	5	29 **	0.001	3.77** (1.64, 8.68)	0.004
All non-cancers	7646	85 ***	<.001	8059	83 ***	<.001	1.02 (1.00, 1.05)	0.070
Circulatory diseases	4394	85 ***	<.001	4605	83 ***	<.001	1.03 (1.00, 1.07)	0.078
Ischemic heart disease	2727	83 ***	<.001	2967	84 ***	<.001	0.99 (0.95, 1.03)	0.652
Cerebrovascular diseases	816	91 **	0.004	792	80 ***	<.001	1.12* (1.03, 1.21)	0.013
Respiratory diseases	1227	78 ***	<.001	1325	77 ***	<.001	1.01 (0.94, 1.07)	0.443
COPD[a]	579	81 ***	<.001	606	78 ***	<.001	1.03 (0.93, 1.13)	0.325
Cirrhosis	145	128 **	0.005	177	148 ***	<.001	0.89 (0.74, 1.07)	0.853
Accidents and violence	566	111 *	0.013	549	105	0.241	1.07 (0.97, 1.19)	0.126
Accidents	394	113 *	0.016	386	109	0.115	1.05 (0.93, 1.18)	0.269
Intentional self-harm	127	130 **	0.005	116	114	0.189	1.17 (0.94, 1.44)	0.116

SMR: standardised against mortality rates for England and Wales for 1952–2017 accounting for calendar year and age; RR: additionally adjusted for service or employer and rank or social class, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, SMR two-sided test, RR: one-sided test that RR is greater than 1.

[a] Includes bronchitis and emphysema and chronic obstructive pulmonary disease deaths.

relative to national rates among participants were cancer of the mouth and pharynx, and pleural cancer (SMRs of 133 and 129 respectively); while for controls, cancers of mouth and pharynx (SMR = 147) and cancer of the kidney and ureter (SMR = 125) showed an excess. An elevated RR for the participants, based on significance tests at the 5% level, arose only for cancers of the stomach (RR = 1.20, 90% CI 1.00–1.43, $p = 0.049$),prostate (RR = 1.16, 90% CI 1.03–1.30, $p = 0.017$) and respiratory system (RR = 1.07, 90% CI 1.00–1.14, $p = 0.049$). Cancers of the kidney and ureter was the only cancer site to show any evidence of lowered rates in the participants relative to controls (RR = 0.80, 90% CI 0.65–0.99, $p = 0.96$).

For the grouping of all cancers, there was strong evidence that the mortality rates among both participants and controls were lower than national rates in the period up to the end of 1998 (table 2). However, in the following 19 years, SMRs in participants were slightly higher than previously seen and the same as national levels (SMR = 100). The SMR for the control group also increased during this period but it remained just below the national rate (SMR = 96, $p = 0.03$). This pattern was reflected in the RR estimates for all cancers combined. The mortality rate among participants was consistent with the corresponding rate among controls up to the end of 1998 (RR = 1.01, 90% CI 0.96–1.08) but there was weak evidence of a raised

Table 2. Observed numbers of deaths and SMRs among test participants and controls, with RRs of mortality among test participants compared with controls, for selected causes of death and by calendar period.

	Calendar period up to 31/12/1998						Calendar period up 1999–2017					
	Participants		Controls		Mortality rates in test participants relative to controls		Participants		Controls		Mortality rates in test participants relative to controls	
Cause of death	Obs	SMR	Obs	SMR	RR (90% CI)	*p*-val	Obs	SMR	Obs	SMR		*p*-val
All causes	4894	88 ***	5217	87 ***	1.01 (0.98, 1.05)	0.249	7012	91 ***	7332	88 ***	1.03* (1.00, 1.06)	0.035
All neoplasms	1558	93 **	1663	92 ***	1.02 (0.96, 1.08)	0.322	2560	100	2640	96 *	1.04 (0.99, 1.09)	0.077
All cancers	1537	93 **	1642	92 **	1.01 (0.96, 1.08)	0.340	2501	100	2571	96 *	1.04 (1.00, 1.09)	0.064
Benign and unspecified	18	70	21	76	0.96 (0.56, 1.64)	0.550	45	84	57	99	0.85 (0.61, 1.18)	0.798
Buccal cavity and pharynx	36	119	44	136	0.89 (0.61, 1.28)	0.705	38	114	50	141 *	0.83 (0.58, 1.18)	0.810
Mouth and pharynx	28	135	33	149 *	0.93 (0.61, 1.42)	0.611	28	131	33	146 *	0.90 (0.59, 1.37)	0.663
Stomach	92	77 *	92	71 ***	1.09 (0.85, 1.39)	0.289	90	87	73	65 ****	1.33* (1.03, 1.73)	0.034
Liver and gallbladder	25	84	22	69	1.21 (0.74, 1.96)	0.261	78	102	92	112	0.91 (0.70, 1.17)	0.739
Liver cancer	23	100	17	69	1,48 (0.87, 2.52)	0.110	72	105	82	111	0.93 (0.71, 1.22)	0.666
Respiratory system	509	87 **	570	90 *	0.98 (0.89, 1.08)	0.626	776	111 **	735	98	1.13** (1.04, 1.23)	0.007
Lung	463	84 ***	532	89 **	0.95 (0.86, 1.06)	0.766	675	110 *	631	96	1.14** (1.04, 1.25)	0.008
Pleural cancer	19	167 *	10	83	2.09* (1.10, 3.98)	0.030	77	122	80	118	1.07 (0.83, 1.40)	0.328
Melanoma	29	164 *	27	145	1.14 (0.74, 1.78)	0.307	31	104	36	113	0.96 (0.64, 1.45)	0.558
Non-melanoma skin cancer	3	74	0	0 *	NC	NC	14	127	12	100	1.26 (0.66, 2.41)	0.278
Prostate	109	115	100	96	1.21 (0.96, 1.53)	0.085	335	99	318	87 **	1.14* (1.00, 1.30)	0.046
Bladder	53	96	34	56 ***	1.74** (1.21, 2.50)	0.006	101	92	111	93	0.99 (0.79, 1.25)	0.519
Kidney and ureter	42	103	63	145 **	0.72 (0.52, 1.00)	0.951	65	97	81	112	0.86 (0.65, 1.13)	0.813
Brain and CNS	66	109	60	94	1.16 (0.86, 1.55)	0.209	50	95	63	112	0.82 (0.60, 1.13)	0.847
Multiple myeloma	22	95	18	72	1.40 (0.83, 2.37)	0.147	39	81	53	102	0.78 (0.55, 1.10)	0.884
Leukaemia	46	100	33	68 *	1.44 (0.98, 2.11)	0.058	68	89	71	86	1.01 (0.76, 1.34)	0.475
Leukaemia excluding CLL	41	108	23	58 **	1.82* (1.18, 2.82)	0.012	55	98	56	93	1.04 (0.76, 1.42)	0.425
Acute lymphatic (ALL)	5	106	3	62	1.47 (0.42, 5.17)	0.307	4	209	2	98	2.12 (0.51, 8.85)	0.193
Chronic lymphatic (CLL)	5	59	10	108	0.56 (0.23, 1.39)	0.851	13	63	15	67	0.91 (0.49, 1.71)	0.595
Acute myeloid (AML)	26	120	15	66	1.78* (1.03, 3.07)	0.040	39	97	45	105	0.92 (0.64, 1.32)	0.650
Chronic myeloid (CML)	8	98	1	12 **	8.52* (1.48, 49.07)	0.022	10	129	4	48	2.60 (0.98, 6.90)	0.053

(Continued.)

Table 2. (Continued.)

	Calendar period up to 31/12/1998						Calendar period up 1999–2017					
	Participants		Controls		Mortality rates in test participants relative to controls		Participants		Controls		Mortality rates in test participants relative to controls	
Cause of death	Obs	SMR	Obs	SMR	RR (90% CI)	*p*-val	Obs	SMR	Obs	SMR		*p*-val
All non-cancers	3219	84 ***	3390	82 ***	1.02 (0.98, 1.07)	0.172	4427	86 ***	4669	83 ***	1.02 (0.99, 1.06)	0.126
Circulatory diseases	2076	82 ***	2216	81 ***	1.01 (0.96, 1.07)	0.321	2318	88 ***	2389	84 ***	1.05 (1.00, 1.10)	0.064
Ischemic heart disease	1452	81 ***	1594	82 ***	0.98 (0.93, 1.04)	0.677	1275	87 ***	1373	87 ***	1.00 (0.94, 1.06)	0.530
Cerebrovascular diseases	311	87 *	328	83 ***	1.03 (0.90, 1.17)	0.365	505	93	464	79 ***	1.18** (1.06, 1.31)	0.005
Respiratory diseases	320	66 ***	350	65 ***	0.99 (0.87, 1.13)	0.528	907	83 ***	975	82 ***	1.01 (0.94, 1.09)	0.415
COPD[a]	160	67 ***	170	64 ***	1.01 (0.84, 1.21)	0.482	419	89 *	436	86 **	1.03 (0.92, 1.16)	0.308
Cirrhosis	75	136 *	93	159 ***	0.89 (0.69, 1.15)	0.781	70	120	84	137 **	0.89 (0.68, 1.16)	0.760
Accidents and violence	435	121 ***	416	115 **	1.08 (0.96, 1.21)	0.143	131	88	133	83 *	1.06 (0.86, 1.29)	0.329
Accidents	302	133 ***	280	125 ***	1.09 (0.95, 1.26)	0.151	92	76 **	106	81 *	0.93 (0.73, 1.17)	0.698
Intentional self-harm	102	132 **	95	118	1.14 (0.90, 1.44)	0.180	25	122	21	97	1.28 (0.79, 2.09)	0.199

(SMR: standardised against mortality rates for England and Wales for 1952–2017 accounting for calendar year and age; RR: additionally adjusted for service or employer and rank or social class, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, SMR two-sided test, RR: one-sided test that RR is greater than 1.

[a] Includes bronchitis and emphysema and chronic obstructive pulmonary disease deaths.

total cancer mortality rate among participants in the more recent period of follow-up (RR = 1.04, 90% CI 1.00–1.09, $p = 0.06$).

When examining the mortality results by specific cancer types, the observed increase in the all cancer RR estimate in the recent period can be seen to be driven by increased rates for lung cancer (RR = 1.14, 90% CI 1.04–1.25, $p = 0.008$), stomach cancer (RR = 1.33, 90% CI 1.03–1.73, $p = 0.03$) and prostate cancer (RR = 1.14, 90% CI 1.00–1.30, $p = 0.046$). For both prostate and stomach cancer the raised rates are consistent with the estimated RRs during the earlier period and there is no evidence that the mortality rates of participants are above those observed nationally during the more recent period. However, for lung cancer, while there was no evidence of raised rates in the earlier period (RR = 0.95), it is the only cancer site to show good evidence of raised rates compared with the national population over the more recent period (SMR = 110, $p = 0.02$).

3.3. Cancer incidence excluding leukaemia

For all cancers combined, the incidence rates in both participant and control groups were consistent with those of men of the same ages in the national population (SIRs of 101 in both instances, table 3). When comparing participants with controls, there was almost no difference in the incidence rates between the groups (RR = 1.01, 90% CI 0.98–1.04). The 1% difference observed is somewhat lower than the 3% difference noted for cancer mortality. However, some differences are not unexpected as the number of incident cancers is more than 50% greater than the number of cancer deaths (6683 compared to 4038).

Among the specific cancer types considered, the incidence rates were significantly lower than national rates only for stomach cancer (amongst the participants and controls) and benign and unspecified tumours (controls only). The only cancer sites to show evidence of excesses relative to national rates among test participants were cancers of the buccal cavity and pharynx, mouth and pharynx, melanoma, non-melanoma skin cancer, pleural cancer and benign cancers of the brain and central nervous system (CNS) cancers. For all these cancer types, except benign brain and CNS cancers, similarly raised rates were also observed for the control group.

Evidence of a raised RR for the participants arose only for stomach cancer (RR = 1.16, 90% CI 1.00–1.35, $p = 0.05$), for bladder cancer (RR = 1.14, 90% CI 1.01–1.27, $p = 0.03$) and for benign and unspecified tumours (RR = 1.10, 90% CI 1.01–1.21, $p = 0.04$). For both stomach and bladder cancer the estimated RR was similar to that observed for mortality, although in each case the number of incident cases was much greater than the number of deaths.

Unlike the mortality analysis, no excess was observed for incidence of prostate cancer in the participants relative to the controls (RR = 1.01, 90% CI 0.95–1.07) although the power to detect a difference was much greater in the incidence analysis (1418 cases and 444 deaths in participants). The only cancer site where there was some evidence of a lowered RR, for participants relative to controls, was for cancer of the kidney and ureter (RR = 0.83, 90% CI 0.71–0.96, $p = 0.98$) which was primarily driven by raised rates in the controls (SIR = 126, $p < 0.001$) rather than lowered rates in the participants (SIR = 104).

For the grouping of all cancers, incidence rates among both participants and controls were consistent with national rates in the period up to the end of 1998 (SIRs of 99 and 98 respectively, table 4) and this remained the case during the latest follow up period 1999–2016 (SIRs of 103 and 102 respectively). This pattern was reflected in the RR estimates with the incidence rate among participants for all cancers combined consistent with the corresponding rate among controls up to the end of 1998 (RR = 1.01, 90% CI 0.97–1.06) and during the more recent period of follow-up (RR = 1.01, 90% CI 0.98–1.05).

The results for incidence of specific cancer types show that there was evidence of a higher rate in participants relative to controls during the latest follow-up period for lung cancer (RR = 1.09, 90% CI 1.00–1.19, $p = 0.045$); this mirrors that for mortality (RR = 1.14, $p = 0.008$). However, there is no evidence of a difference in rates between the groups in the earlier period (RR = 0.97). Furthermore, lung cancer is one of the few sites to show evidence of a raised rate among participants, when compared with the national population, over the more recent period (SIR = 111, $p = 0.004$), while the rate in the controls is close to the national rate.

For the cancer sites that showed increased cancer incidence rates among the participants, over the whole period of follow-up relative to national rates (i.e. cancer of the buccal cavity and pharynx, mouth and pharynx, melanoma, non-melanoma skin cancer, pleural cancer and benign brain and CNS cancers) there were no marked differences in estimates between the earlier and later periods except that the evidence of raised pleural cancers in the later period was more limited ($p = 0.09$, table 4)). Similarly, for bladder and stomach cancers where an increased RR was observed for participants over the whole follow-up period, there was no evidence that this raised risk differed between the later (RRs of 1.13 and 1.22) and earlier periods (RRs of 1.15 and 1.10). The raised rate of benign and unspecified tumours among the participants relative to controls observed over the whole follow-up period was mainly driven by increases in the earlier period

Table 3. Observed numbers of cancers and SIRs among test participants and controls, with RRs of cancer incidence among test participants compared with controls, for selected types of cancer and leukaemia over the whole follow-up period.

	Participants			Controls			Incidence rates in test participants relative to controls	
Types of cancer [a]	Obs	SIR	*p*-val	Obs	SIR	*p*-val	RR (90% CI)	*p*-val
All neoplasms	9597	105 ***	<.001	10 210	104 ***	<.001	1.01 (0.99, 1.03)	0.271
All cancers	6683	101	0.273	7087	101	0.652	1.01 (0.98, 1.04)	0.257
Benign and unspecified	669	98	0.560	653	89 **	0.003	1.10* (1.01, 1.21)	0.039
Buccal cavity and pharynx	165	119 *	0.034	198	134 ***	<.001	0.90 (0.76, 1.08)	0.828
Mouth and pharynx	105	127 *	0.021	123	140 ***	<.001	0.93 (0.75, 1.16)	0.704
Stomach	255	88 *	0.038	235	75 ***	<.001	1.16* (1.00, 1.35)	0.050
Liver and gallbladder	178	103	0.727	182	98	0.846	1.06 (0.89, 1.26)	0.295
Liver	154	108	0.363	153	100	0.996	1.09 (0.91, 1.32)	0.216
Respiratory system	1506	103	0.326	1556	99	0.729	1.04 (0.98, 1.10)	0.144
Lung	1255	99	0.748	1290	95	0.071	1.04 (0.98, 1.11)	0.148
Pleural cancer	120	130 **	0.007	137	139 ***	<.001	0.97 (0.79, 1.20)	0.586
Melanoma	192	128 **	0.001	199	125 **	0.003	1.05 (0.89, 1.24)	0.305
Non-melanoma skin cancer	2245	121 **	<.001	2470	124 ***	<.001	0.98 (0.93, 1.03)	0.788
Prostate	1418	101	0.697	1512	101	0.770	1.01 (0.95, 1.07)	0.428
Bladder	428	102	0.628	409	91	0.066	1.14* (1.01, 1.27)	0.033
Kidney and ureter	212	104	0.550	273	126 ***	<.001	0.83 (0.71, 0.96)	0.982
Brain and CNS	146	112	0.194	147	106	0.482	1.05 (0.87, 1.27)	0.337
Benign brain and CNS	43	208 ***	<.001	23	105	0.872	1.97** (1.29, 3.02)	0.004
Multiple myeloma	102	96	0.702	112	98	0.895	0.98 (0.78, 1.23)	0.554
Leukaemia	191	112	0.128	169	93	0.344	1.19 (1.00, 1.42)	0.051
Leukaemia excluding CLL	116	116	0.126	89	83	0.086	1.38* (1.10, 1.75)	0.011
Acute lymphatic (ALL)	9	144	0.362	8	120	0.707	1.23 (0.55, 2.75)	0.333
Chronic lymphatic (CLL)	75	106	0.617	80	106	0.626	0.98 (0.75, 1.27)	0.557
Acute myeloid (AML)	59	103	0.839	51	84	0.218	1.22 (0.89, 1.68)	0.146
Chronic myeloid (CML)	32	151 *	0.034	14	62	0.072	2.43** (1.43, 4.13)	0.003

[a] Non-melanoma skin cancers (NMSC) events are only counted as events in the all neoplasm and NMSC groupings. SIR: standardised against incidence rates for England and Wales for 1971–2006 and England for 2007–2016, accounting for calendar year and age; RR: additionally adjusted for service or employer and rank or social class, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, SIR two-sided test, RR: one-sided test that RR is greater than 1.

(RR = 1.35, 90% CI 1.09–1.67), with little evidence of higher rates after 1998 (RR = 1.05). When examining subtypes of benign and unspecified tumours, the increased rate in participants was partially driven by benign tumours of the brain and central nervous system (CNS), where incidence rates were higher than both national levels (SIR = 208, $p < 0.001$, based on 43 cases) and those observed amongst the control group (SIR = 105 for controls based on 23 cases, RR = 1.97, 90%CI 1.29–3.02, $p = 0.004$).

3.4. Leukaemia mortality

For all leukaemias, the mortality rate among participants was consistent with national levels (SMR = 93, $p = 0.45$) (table 1), while the control group showed evidence of rates that were lower than that in men of the same ages in England and Wales (SMR = 79, $p = 0.02$). Comparing participants with controls, the RR for all leukaemia was 1.14 (90% CI 0.91–1.43, $p = 0.16$), providing only weak evidence of a difference between the groups. For leukaemia excluding chronic lymphatic (non-CLL), the participants' mortality rate was consistent with the national level (SMR = 102), while the controls' rate remained below that observed nationally (SMR = 79, $p = 0.04$). The excess RR for non-CLL was slightly higher than for all leukaemia (26% compared to 14%), which is suggestive of raised rates in participants compared to controls at a borderline level of significance (RR = 1.26, 90% CI 0.98–1.61, $p = 0.06$).

There was no evidence of increased risks relative to national rates among participants or controls for any of the leukaemia sub-types (table 1). For the participant group only, CLL mortality showed evidence of low rates when compared with national figures, while for the control group only, CML rates showed evidence of a low rate in comparison with the national population. There was strong evidence that the RR of mortality among participants compared with controls was raised for CML (RR = 3.77, 90% CI 1.64–8.68, $p = 0.004$), but the rate of CML among participants was consistent with national levels (SMR = 113, $p > 0.5$), so much of the evidence for the raised RR can be attributed to the very low rate of CML seen amongst the controls (SMR = 29, $p = 0.001$).

Table 4. Observed numbers of cancers and SIRs among test participants and controls, with RRs of cancer incidence among test participants compared with controls, for selected types of cancer and by calendar period.

	Calendar period up to 31/12/1998						Calendar period up 1999–2016					
	Participants		Controls		Incidence rates in test participants relative to controls		Participants		Controls		Incidence rates in test participants relative to controls	
Types of cancer [a]	Obs	SIR	Obs	SIR	RR (90% CI)	*p*-val	Obs	SIR	Obs	SIR	RR (90% CI)	*p*-val
All neoplasms	2934	102	3173	103	1.00 (0.96, 1.04)	0.538	6663	107 ***	7037	105 ***	1.01 (0.99, 1.04)	0.212
All cancers	2326	99	2476	98	1.01 (0.97, 1.06)	0.319	4357	103	4611	102	1.01 (0.98, 1.05)	0.321
Benign and unspecified	134	106	109	81 *	1.35* (1.09, 1.67)	0.011	535	96	544	91 *	1.05 (0.95, 1.17)	0.191
Buccal cavity and pharynx	75	117	91	134 **	0.89 (0.69, 1.16)	0.761	90	120	107	135 **	0.91 (0.72, 1.16)	0.735
Mouth and pharynx	49	124	62	148 **	0.87 (0.63, 1.19)	0.766	56	129	61	133 *	0.99 (0.73, 1.35)	0.514
Stomach	115	80 *	113	73 ***	1.10 (0.88, 1.37)	0.242	140	95	122	78 **	1.22 (0.99, 1.49)	0.058
Liver and gallbladder	55	94	57	90	1.08 (0.79, 1.48)	0.337	123	108	125	102	1.05 (0.85, 1.29)	0.351
Liver	52	109	51	100	1.15 (0.83, 1.60)	0.235	102	107	102	100	1.07 (0.85, 1.34)	0.323
Respiratory system	594	90 *	653	92 *	0.98 (0.89, 1.08)	0.626	912	113 ***	903	105	1.08 (1.00, 1.17)	0.050
Lung	493	85 ***	545	87 **	0.97 (0.88, 1.08)	0.662	762	111 **	745	102	1.09* (1.00, 1.19)	0.045
Pleural cancer	36	156 *	35	142	1.16 (0.78, 1.71)	0.271	84	121	102	137 **	0.91 (0.71, 1.16)	0.735
Melanoma	59	149 **	60	143 *	1.08 (0.79, 1.46)	0.346	133	121 *	139	119	1.04 (0.85, 1.28)	0.363
Non-melanoma skin cancer	474	116 **	588	134 ***	0.86 (0.78, 0.96)	0.990	1771	122 ***	1882	121 ***	1.01 (0.96, 1.07)	0.364
Prostate	289	121 **	270	104	1.18* (1.02, 1.35)	0.029	1129	97	1242	100	0.97 (0.91, 1.04)	0.761
Bladder	176	98	167	87	1.15 (0.97, 1.38)	0.094	252	106	242	95	1.13 (0.97, 1.31)	0.094
Kidney and ureter	69	100	108	147 ***	0.68 (0.53, 0.88)	0.994	143	107	165	115	0.92 (0.76, 1.11)	0.767
Brain and CNS	81	118	71	98	1.23 (0.94, 1.61)	0.100	65	105	76	116	0.89 (0.67, 1.17)	0.763
Benign brain and CNS	21	188 *	9	76	2.49* (1.29, 4.81)	0.011	22	231 ***	14	138	1.64 (0.94, 2.88)	0.074
Multiple myeloma	36	109	37	105	1.08 (0.73, 1.59)	0.378	66	90	75	95	0.94 (0.71, 1.24)	0.653
Leukaemia	74	127	51	82	1.54** (1.14, 2.08)	0.009	117	104	118	99	1.04 (0.84, 1.29)	0.388
Leukaemia excluding CLL	45	119	32	80	1.49* (1.01, 2.18)	0.045	71	114	57	86	1.32 (0.99, 1.78)	0.058
Acute lymphatic (ALL)	5	118	6	132	0.93 (0.34, 2.52)	0.548	4	198	2	93	2.10 (0.51, 8.77)	0.196
Chronic lymphatic (CLL)	29	140	19	85	1.63* (1.00, 2.66)	0.049	46	93	61	115	0.78 (0.56, 1.07)	0.903
Acute myeloid (AML)	26	134	13	63	2.06* (1.17, 3.61)	0.018	33	88	38	94	0.94 (0.63, 1.39)	0.607
Chronic myeloid (CML)	11	128	6	65	1.96 (0.84, 4.55)	0.096	21	167 *	8	59	2.78** (1.40, 5.52)	0.007

[a] Non-melanoma skin cancers (NMSC) events are only counted as events in the all neoplasm and NMSC groupings. SIR: standardised against incidence rates for England and Wales for 1971–2006 and England for 2007–2016, accounting for calendar year and age; RR: additionally adjusted for service or employer and rank or social class, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, SIR two-sided test, RR: one-sided test that RR is greater than 1.

The all leukaemia mortality rate among participants was consistent with national levels both in the period up to 1998 (SMR = 100, table 2) and during the period 1999–2017 (SMR = 89), while in the control group, rates were lower than national levels in the period up to the end of 1998 (SMR = 68, $p = 0.02$), but increased slightly to become consistent with national rates during the period 1999–2017 (SMR = 86, $p = 0.22$). There was borderline significant evidence that the all leukaemia mortality rate among participants was higher than in the control group in the period up to 1998 (RR = 1.44, $p = 0.06$), but no evidence that this increased risk persisted in the more recent period of follow-up (RR = 1.01, 90% CI 0.76–1.34). For non-CLL, the pattern of results was very similar to that observed for all leukaemia with rates consistent with national levels apart from controls in the earlier follow-up period, where the non-CLL rate was below that observed nationally (SMR = 58, $p = 0.006$). For the period up to 1998, there was stronger evidence that the non-CLL risk in the participants was higher than that among the controls (RR = 1.82, 90% CI 1.18–2.82, $p = 0.01$), but there was little evidence that this increase extended to the more recent follow-up period (RR = 1.04, 90% CI 0.76–1.42, $p = 0.43$).

When examining the results by specific leukaemia sub-types and calendar period, there was no evidence of mortality rates being different (either above or below) from national levels in either the earlier or later follow-up periods. The only exception to this was the low level of CML seen in the control group during the earlier follow-up period (SMR = 12, $p = 0.004$). The increased risk of non-CLL found in participants, relative to the controls, in the earlier follow-up period was driven by the findings for AML (RR = 1.78, 90% CI 1.03–3.07, $p = 0.04$) and CML (RR = 8.52, 90% CI 1.48–49.07, $p = 0.02$). For AML, there was no evidence that the increased rate continued into the more recent period (RR = 0.92), however, for CML, there does remain some evidence that increased risk may have persisted with extended follow-up (RR = 2.60, 90% CI 0.98–6.90, $p = 0.05$).

3.5. Leukaemia incidence

For all leukaemia, the incidence rate in both participants and controls was consistent with national rates (SIRs of 112 and 93 respectively, table 3). The RR for all leukaemia was 1.19 (90% CI 1.00–1.42, $p = 0.05$). For non-CLL leukaemia, the participants' incidence rate was raised though consistent with the national rate (SIR = 116, $p = 0.13$), while the controls' rate was a little below the expected rate (SIR = 83, $p = 0.09$). Consequently, the RR for non-CLL leukaemia was higher than for all leukaemia and the evidence of a difference between the groups was stronger (RR = 1.38, 90% CI 1.10–1.75, $p = 0.01$).

Unlike for mortality, there was no evidence that incidence rates fell below those expected based on national rates for any of the leukaemia sub-types for either test participants or controls. The only leukaemia sub-type to show evidence of an excess relative to national rates was CML among participants (SIR = 151, $p = 0.03$, 32 cases). The evidence for raised RRs for most leukaemia sub-types was limited, however there was strong evidence of a raised RR for CML (RR = 2.43, 90% CI 1.43–4.13, $p = 0.003$). This tallies with the findings from the mortality analysis although the number of CML cases amongst participants was greater in the incidence analysis (32 cases compared with 18 deaths).

Table 4 shows that for all leukaemia, the incidence rate among participants was higher than, though statistically consistent with, the national rate both in the period up to 1998 (SMR = 127, $p = 0.06$) and during 1999–2016 (SIR = 104, $p > 0.5$). In the control group, the rate was lower than, though consistent with, national rates both in the period up to the end of 1998 (SIR = 82, $p = 0.16$) and during 1999–2016 (SIR = 99, $p > 0.5$). As was observed for mortality, there was some evidence that the all leukaemia incidence rate among participants was higher than that in the control group in the period up to 1998 (RR = 1.54, 90% CI 1.14–2.08, $p = 0.01$). However, there was very little evidence that this increased risk had persisted in the more recent period of follow-up (RR = 1.04, 90% CI 0.84–1.29, $p = 0.39$). For non-CLL, the pattern of results was very similar with rates for both participants and controls consistent with national levels in both the earlier and later periods. There was some evidence of increased rates of non-CLL in participants compared with controls (RR = 1.49, 90% CI 1.01–2.18, $p = 0.04$) in the earlier follow-up period, which, in contrast to the mortality analysis, persisted in the more recent follow-up period (RR = 1.32, 90% CI 0.99–1.78, $p = 0.06$).

Among leukaemia sub-types, there was no evidence that incidence rates differed (either above or below) from national levels in either the earlier or later follow-up periods except for a raised level of CML seen in the participants during the later period (SIR = 167, $p = 0.04$). The raised risk of both all leukaemia and non-CLL seen in participants (relative to the controls) in the earlier period was driven by the findings for AML (RR = 2.06, 90% CI 1.17–3.61, $p = 0.02$), CML (RR = 1.96, 90% CI 0.84–4.55, $p = 0.10$) and CLL (RR = 1.63, 90% CI 1.00–2.66, $p = 0.05$), where a raised RR was seen for the period up to 1998. For AML and CLL, there was no evidence that the increased rates continued in the more recent period (RR of 0.94 and 0.78 respectively), however, for CML the evidence of increased risk has strengthened with extended follow-up (RR = 2.78, 90% CI 1.40–5.52, $p = 0.01$).

3.6. Non-cancer mortality

For all non-cancers (table 1), there was strong evidence that the mortality rates in both participants and controls were lower than expected (SMRs of 85 and 83 respectively, $p < 0.001$). Mortality among both the participants and controls was lower than national rates for most of the specific diseases considered. The only causes of death that showed evidence of an excess relative to national rates among participants were cirrhosis (SMR = 128, $p = 0.005$) and accidents and violence (SMR = 111, $p = 0.01$). While cirrhosis rates are high, it should be noted that an even greater excess, relative to national rates, was observed for cirrhosis in the control group (SMR = 148, $p < 0.001$). The increased rate of accidents and violence is driven by raised rates of death associated with the sub-groups of accidents (SMR = 113, $p = 0.02$) and acts of intentional self-harm (SMR = 130, $p = 0.005$). Although raised rates of deaths associated with accidents (SMR = 109, $p = 0.12$) and acts of intentional self-harm (SMR = 114, $p = 0.19$) were also observed in the control group, they were statistically compatible with national levels. The only disease that showed some evidence of raised RR for the participants was cerebrovascular disease (RR = 1.12, 90% CI 1.03–1.21, $p = 0.01$). For both cirrhosis (RR = 0.89, 90% CI 0.74–1.07, $p = 0.15$) and accidents and violence (RR = 1.07, 90% CI 0.97–1.19, $p = 0.13$) there was little evidence that mortality rates in participants was different to that in the controls.

For all non-cancer causes of death combined, mortality rates among both participants and controls were lower than national rates in the period up to the end of 1998 and this remained the case during the period 1999–2017 with rates between 14 and 18% lower than national levels (table 2). The overall mortality rate among participants for all non-cancers combined was consistent with the corresponding rate among controls up to the end of 1998 (RR = 1.02, 90% CI 0.98–1.07, $p = 0.17$) and this remained unchanged in the more recent period of follow-up (RR = 1.02, 90% CI 0.99–1.06, $p = 0.13$). The observed increase in cerebrovascular diseases, for the participants relative to controls, seen across the whole period, was driven by increased rates for the later period (RR = 1.18, 90% CI 1.06–1.31, $p = 0.005$), with little evidence of elevated rates in the earlier period (RR = 1.03, 90% CI 0.90–1.17, $p = 0.36$). However, there is no evidence that the mortality rate of participants was above that observed nationally during either the earlier or later period (SMRs of 87 and 93 respectively).

3.7. Mortality and cancer incidence in test participants by type and degree of exposure (see supplementary material for results relevant to this section)

Among the 23% of test participants known to have been monitored for exposure to radiation, cancer incidence rates were similar to national rates, irrespective of whether a non-zero gamma dose had been recorded (supplementary table S6). There was also no evidence that participants with a positive recorded dose had raised incidence rates when compared with participants with a zero recorded dose for the group of all cancers (RR = 1.04, $p = 0.26$). The only cancer site where evidence of a raised incidence rate was noted for participants with a positive recorded gamma dose was for non-melanoma skin cancers (NMSC, RR = 1.26, $p = 0.01$). For NMSC, the rate among those with non-zero dose was raised above the national level (SIR = 133) which is not dissimilar to the rate found for either the participants as whole (SIR = 121) or in the control group (SIR = 124). The elevated RR of 1.26 is a consequence of the lower rate observed in the participants with a zero recorded dose although their rates are still raised (SIR = 111). For multiple myeloma, there was little evidence that participants with a positive dose had a higher incidence rate than those with zero recorded dose (RR = 1.68, 90% CI 0.78–3.61, $p = 0.13$). The rates of myeloma in these two groups were based on a small number of cases and there was no evidence that rates were different to those observed nationally. For leukaemia there was no evidence that participants with a positive recorded dose had raised incidence rates when compared with participants with a zero recorded dose for either all leukaemia (RR = 0.70, $p = 0.84$) or non-CLL (RR = 0.41, $p = 0.95$) For non-CLL, there was evidence ($p = 0.046$) that the incidence was higher among monitored participants with zero recorded dose (SIR = 121) than among those with a positive gamma dose (SIR = 58). As with the myeloma analysis, the rates of leukaemia in these two groups were based on small numbers of cases. The fact that only 23% of participants were monitored for radiation, of whom 64% had zero recorded dose, limits the power of these comparisons.

Amongst participants who were monitored for radiation exposure there was no evidence of increasing risks with dose (supplementary table S7) apart from for NMSC. For NMSC, the evidence of an increase was strong ($p = 0.005$), with the rate for participants receiving more than 50 mSv, more than twice that predicted if there was no association with dose (14 cases compared to 6.9 expected). There was some weak evidence of an increasing trend in multiple myeloma incidence with increasing dose ($p = 0.071$), but this finding was based on only 11 multiple myeloma cases with a positive dose, of which only three had a recorded dose more than 10 mSv. There was no evidence of a trend in the risk with dose for leukaemia. The direction of the point estimate of the trend is negative and there is only a single recorded non-CLL among the participants with a recorded dose greater than 10 mSv.

Among those participants who were present at a major operation, the incidence rate for all cancers combined was consistent with the national rate and this was also true for all cancer sub-types apart from NMSC, melanoma and pleural cancers which were all raised relative to national rates, a pattern also observed in the full cohort of test participants (supplementary table S8). The RR analysis (supplementary table S9) suggests that non-leukaemic cancer incidence rates, in those participants who attended a major operation, were generally consistent with those amongst the control group, with only stomach cancer higher among the major operation participants compared to the control group. When examining the experience of participants who were present at a major operation in the Pacific and Australia separately (supplementary table S10) the pattern of results was unchanged with little evidence of a difference based on test location.

Generally similar findings arose among men identified by MOD as being more liable to exposure to radiation (identified in tables S8 and S9 as Group A), and for participants employed by AWE or who were directly involved in the minor trials at Maralinga (referred to in tables S8 and S9 as Group B, the group most likely to have been exposed to internal radionuclides), although the numbers of incident cancers in these groups were much smaller. However, for both prostate cancer and brain and CNS tumours the incidence rates were higher than national rates in both Groups A (brain SIR = 199, $p = 0.08$; prostate SIR = 138, $p = 0.01$) and B (brain SIR = 217, $p = 0.01$; prostate SIR = 131, $p = 0.01$). The rates in both groups were also raised when compared with controls: RRs of 1.36 ($p = 0.01$) and 1.39 ($p = 0.02$) for prostate cancer in Groups A and B respectively; RRs of 1.94 ($p = 0.04$) and 2.18 ($p = 0.03$) for tumours of the brain and CNS in Groups A and B respectively. Evidence of raised incidence rates for NMSC in each of the groups was also observed, which was comparable to that found among all participants.

The rates of both all leukaemia and non-CLL were statistically compatible with national levels for each of the sub-groups considered. For both all leukaemia and non-CLL, the highest sub-group incidence rate was observed in special exposure group A. For all leukaemia, the raised rate reached borderline significance (SIR = 184, $p = 0.07$, 12 cases) in this group and there was evidence that the rate differed from that in the control group (RR = 2.12, 90%CI: 1.24–3.63, $p = 0.02$). For non-CLL incidence, the number of cases was small (6 cases) and the evidence of raised rates was weaker (SIR = 157, $p = 0.37$). The evidence that the non-CLL rate in this group differed from that in the control group (RR = 1.81, 90%CI: 0.86–3.80, $p = 0.08$) was of only borderline significance. The only sub-group to show evidence of a raised risk when compared to controls for non-CLL was for participants not in special exposure groups A or B and who were unmonitored for radiation and who were not involved at major operations. Although this group of participants (essentially participants involved in clean-up operations with no radiation record) did have raised rates relative to controls (RR = 1.58, 90% CI 1.08–2.29, $p = 0.03$), their non-CLL incidence rate was consistent with that observed nationally (SIR = 117, $p = 0.46$, 27 cases).

Analyses of subgroups with greater potential for exposure provided little evidence of increased non-cancer disease risks (see supplementary tables S6(a)–S9(a) and S11). The only exception was for cerebrovascular diseases where there was some evidence that risks were higher in participant groups previously identified by MOD as being most liable to exposure (i.e. groups A and B and participants with a positive recorded radiation dose). Although this group of participants did have raised rates relative to controls (RR = 1.22, 90% CI 1.03–1.44, $p = 0.03$) (table S9(a)) their rate was consistent with that observed nationally (SMR = 91, $p = 0.25$, 143 deaths) (table S8(a)).

In addition to the sub-group analyses presented above, a range of sensitivity analyses were also conducted, to check the robustness of the overall findings. These included an examination of differing upper age censoring dates i.e. truncating experience at ages 85, 90, 100 or age no-truncation. These analyses revealed no differences, so the results given are based on findings without age truncation. The final results are based on separate analyses of mortality and cancer incidence end-points but an analysis combining mortality and incidence data was also conducted (as used in prior incidence analysis of this cohort). These results were found to follow the incidence findings very closely, so separate results of this analysis have not been presented. Heterogeneity tests were also conducted to examine whether the estimate of any potential test effect (i.e. the RR estimate) varied across service, rank or by time since test participation. For the disease groups considered, there was no evidence of significant heterogeneity across service and similar results were also obtained for tests of heterogeneity by rank and time since test participation. As the best fitting model for the data is a common RR estimate across rank, service and time since test participation, the RR estimates presented in the paper are based on a model using this assumption. Results of supplementary analyses by service, rank and time since test participation can be found in the supplementary material along with results from the heterogeneity analyses.

4. Discussion

4.1. General considerations

This study further updates the previous three analyses of this cohort with an additional 19 years of follow-up. It aims to detect effects of test participation on mortality and cancer incidence, irrespective of the precise cause, but, given that radiation is a known carcinogen, it does also consider if the recorded radiation exposures of test participants could be a plausible cause of any observed effects. However, if the radiation doses recorded for test participants at the time of their involvement accurately reflect the broad levels of exposure, then, based on both risk factors derived from other groups exposed to radiation (e.g. the INWORKS [16–18], Mayak [19–21] and LSS cohorts [22, 23]) and the radiation protection recommendations of the International Commission for Radiological Protection [24], significantly raised mortality or cancer incidence risks would not be expected to be observed. No evidence has emerged that the recorded doses used in this study are over or under-estimates. However, while many participants were monitored for radiation exposure at the earlier tests (e.g. Hurricane, 96% monitored), for the later tests, only people judged most likely to be exposed appear to have been monitored (e.g. Grapple, 2% monitored). Consequently, only 23% of participants overall had recorded dose estimates, of whom 64% had zero recorded dose, so the power to detect any increasing risks with measured dose was limited. Nevertheless, the analyses should have been able to detect raised risks if, in fact, doses to the groups most likely to have been exposed had been much larger than recorded.

The possibility also exists that test participants suffered ill health caused by exposure to other factors. The identity of any hazardous factor other than radiation that is associated with test participation is likely to depend on the disease in question. Taking leukaemia, as an example, where the number of potential confounders is limited [25], the exposures to these confounders would have to vary greatly between the participants and control group to cause much effect especially as the analyses already adjust for several other baseline factors including age, calendar period, rank and service. Smoking is one potential confounder for myeloid leukaemia [26], but the association is weak, and it difficult to imagine how this could have much impact on risks. Several chemicals are also known to be associated with increased leukaemia risk [27], e.g. benzene, which in a recent review [28] was found to be strongly related to AML. While some exposure to chemicals (including benzene) in the military is likely, the level of these exposures would have to vary between the participant and control group in a consistent way to confound any potential association.

The previous analysis of this cohort, based on follow-up to the end of 1998 [8], concluded that the overall levels of mortality and cancer incidence in participants was similar to that in the matched control group and that, for both groups, overall mortality was lower than expected from national rates. The suggestion from the first analysis [4, 5] that participants may have experienced increased rates of multiple myeloma was not supported by the second or third analyses. However, the third analysis [8] could not completely rule out the possibility that test participation may have caused a small risk of leukaemia in the early years after the tests, which had been observed in both previous analyses.

The following discussion will consider the extent to which the longer follow-up, to the end of 2017, has modified the previous conclusions.

4.2. Overall mortality and cancer incidence

Both the test participants and the control group continue to show strong evidence that they are healthier than the general population with mortality rates 10% and 12% below those expected based on national rates. These veterans have now been followed for up to 65 years, during which time just over half, nearly 12 000 (56%), of them have died; the average age of those remaining alive is 81 years. The lower overall mortality rate was mainly due to lower rates of non-cancer diseases, particularly heart and respiratory diseases (SMR = 83, $p < 0.001$ and SMR = 78, $p < 0.001$ respectively). These lower rates are likely to be due to selection factors on recruitment into the services i.e. a person must be physically fit to qualify for service. This 'healthy soldier effect' (HSE) [14] has persisted for many decades after initial selection for non-cancer diseases as even in the sixth decade of follow-up the non-cancer death rates remain 17% and 18% below national levels for the participants and controls respectively (tables S17(b) and (c)). The strength of the HSE on cancer outcomes is more limited and amongst participants there is now no evidence that overall cancer mortality or incidence rates are below those observed nationally (SMR = 97 and SIR = 101). The SMRs and SIRs for all cancer in the participants were below those observed nationally for the first three decades of follow-up (SMR = 82, $p < 0.001$ and SIR = 90, $p = 0.003$, tables S16(d) and (b)), but there was no evidence of lower rates thereafter (SMR = 100 and SIR = 103, tables S16(d) and (b)). This pattern of a persistent HSE for non-cancer diseases and a reducing HSE for cancer diseases was also observed in the ongoing studies of US atomic test veterans [29], where initial low cancer rates in the first 20 years of follow-up (SMR = 71) eventually increased to levels above those observed in the general population after more than 30 years of follow-up (SMR = 107).

The previous analyses of this cohort [7, 9] showed no evidence of raised rates in participants relative to controls for either all causes of death or all cancers, but this analysis now provides some evidence that the overall mortality level in the test participants is marginally higher (RR 1.02, 90% CI 1.00–1.05, $p = 0.04$) than that in the control group. This evidence is driven by a slightly larger RR (RR 1.03, 90% CI 1.00–1.06, $p = 0.04$) in the more recent period of follow-up (1999–2017). Given the small size of any difference (2% higher mortality rate in participants), it is entirely possible that it may be explained by variation in background characteristics between participants and control groups that could not be accounted for in the analysis. One such characteristic is smoking, which has been observed to be the likely cause of higher rates of certain diseases, when compared to the general population, in a long term study of other UK veterans [30]. However, while lung cancer and cerebrovascular results may support an effect of smoking, results from other smoking related diseases, e.g. ischemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD), do not. This suggests that attributing the difference in overall risk to smoking characteristics alone is not appropriate. In fact, several specific cancers contributed to the evidence of higher rates in participants relative to controls. These include non-CLL leukaemia and cancers of the stomach, bladder, prostate and respiratory organs, which all showed evidence of higher overall mortality or cancer incidence rates than in controls. Prostate, brain and non-melanoma skin cancer also showed some evidence of increased incidence rates in sub-groups with greater potential for exposure. Amongst non-cancer diseases, the overall differences between the participants and controls were also contributed to by cerebrovascular diseases which showed higher mortality rates than in the controls. Some of these findings are discussed in greater detail in the following sections.

4.3. Multiple myeloma

This analysis provides no evidence of an association between participation in the UK nuclear weapons test programme and the risk of multiple myeloma. Although the first analysis [5] of this cohort reported a raised risk of myeloma compared to rates in the control group, in the early years following test participation, it seems likely—as suggested in the second analysis [6, 7]—that this was a chance finding. Analyses of subgroups with greater potential for exposure provided little evidence of increased risks, although, there was some weak evidence, based on small numbers, for a positive trend in risk with dose among the 23% of participants who were monitored for radiation exposure.

4.4. Leukaemia

In the first few years after the atomic bombings of Hiroshima and Nagasaki, more leukaemias were observed among the survivors than expected [31]; this excess has persisted in long-term follow-up studies of the survivors [32–34]. While these studies helped to establish a link between leukaemia and acute radiation exposures, there remains uncertainty over the translation of these risks to different populations and to low-doses exposures. The risk of leukaemia has also been shown to be increased in populations of nuclear workers and several groups who received exposures for medical reasons. Reviews of the relevant literature include those by Daniels *et al* [35], UNSCEAR [36] and NRPB [37]. These studies have linked each of the main sub-types of leukaemia with radiation, except for CLL. While excess risk has been seen to start to increase within a few years of exposure and then to fall with time since exposure, there is evidence from the atomic bomb survivors and nuclear worker studies that small increases in risk can persist many decades after exposure [34].

Studies of radiation workers have indicated an association between occupational radiation exposure and the risk of leukaemia of a magnitude consistent with that predicted from the Japanese A-bomb data [38, 39]. While some studies have suggested a possible link between radiation exposure and CLL [34, 40–42], there is an abundance of evidence from high power studies of a general absence of excess risk for CLL [36, 41]. This study provided no evidence of increased risk of CLL in participants relative to controls for either mortality (RR 0.78, 90% CI 0.47–1.29) or incidence (RR 0.98, 90% CI 0.75–1.27). For these reasons, the discussion that follows focuses on all non-CLL leukaemia and the three other main sub-types of leukaemia: ALL, AML and CML.

The doses received by most participants in the nuclear weapons tests are likely to be lower than those received by radiation workers employed for many years in the nuclear industry. Among the 1716 test participants in this study with a non-zero recorded radiation dose, the mean dose was about 10 mSv, and only 81 participants were recorded as having received 50 mSv or more, whereas the 173 000 radiation workers in the UK National Registry for Radiation Workers had a mean lifetime dose of 25 mSv and doses ranging up to over 1 Sv [39], although approximately two-thirds of this cohort received doses less than 10 mSv. In contrast to studies of radiation workers where all participants are monitored, only 23% of the weapons test participants were monitored for radiation exposure and 64% of these had zero recorded dose, making it hard to detect a raised risk with measured dose amongst these men. However, given that any effect

of test participation might be due to factors other than radiation, it is important in the context of the current analysis to consider results from other studies of nuclear weapon test participants.

In the 'Five Series Study' of about 70 000 US military personnel who took part in at least one out of five selected US nuclear weapons test series in Nevada or the Pacific in the 1950s [43], leukaemia mortality was less than national rates (SMR 74, based on 185 deaths), with some weak evidence of a raised risk relative to a matched control group (RR 1.15, 95% CI 0.93–1.43); similar results were obtained for leukaemia excluding CLL. A more recent update to this study [29], the 'Eight Series Study' of 114 270 military personal, found little evidence of increased leukaemia risks (SMR = 103, based on 663 deaths) or any evidence that leukaemia risks increased with measured dose. Among over 38 000 US Navy personnel who took part in Operation Crossroads at Bikini Atoll in the Pacific in 1946 [44], leukaemia mortality was similar to that in a matched control group (RR 1.02, 95% CI 0.75–1.39). In a study of 8,500 US Navy veterans who took part in Operation Hardtack I in 1958 in the Pacific [45], leukaemia deaths were no greater than expected from national rates, nor were they higher than expected compared to a matched control group, although only six deaths were observed amongst these participants. In contrast, studies of 3,020 US veterans involved at the SMOKY tests have revealed increases in leukaemia [46] which have persisted, although to a reduced degree, with extended follow-up [47]. A study of 10 983 Australian veterans who also participated in the UK tests [48], has shown increases in leukaemia incidence when in comparison with the national population (SMR = 161, based on 47 cases), but there was no evidence that risks increased with reconstructed radiation exposures. Increases in leukaemia risk have also been reported among 528 men from New Zealand who participated in UK atmospheric nuclear weapons tests in the Pacific [49]. Four leukaemia deaths were observed compared with 0.8 expected from national rates, whilst the RR compared to a matched control group was 5.6 (90% CI 1.0–41.7); the corresponding RR for leukaemia incidence among the New Zealand participants was very similar to that for mortality. Although few leukaemias were seen in some of these studies, there are some suggestions from the Australian, New Zealand and some US veteran studies of a raised risk.

The first three analyses of the cohort of UK test participants found a raised risk of leukaemia relative to controls. However, in the first analysis, Darby *et al* [4, 5] drew attention to the difficulty in interpreting these results, given that mortality rates in participants were only slightly above national levels, whilst control rates were substantially below them. This pattern is maintained in the current analysis and is also present in the incidence analysis. The non-CLL incidence SIRs for participants and controls over the first 30 years after first test participation (or since start of follow-up in the controls) were 113 and 53 ($p = 0.03$) respectively while for the later period of follow-up (i.e. after the first 30 years of follow-up) the non-CLL SIR is no longer reduced for the control group (SMR = 90, $p = 0.41$) and nearer to that of the participants (SMR = 115, $p = 0.18$, see tables S16(b)–(e) for incidence and mortality results).

It should be noted that the study was set-up in the 1980s with both retrospective and prospective tracing elements and it is during the retrospective tracing period where the rates of non-CLL mortality and incidence rates are very low amongst controls. However, the rates of other diseases amongst participants and controls (including cancers) are very similar during these early years of follow-up, which suggests that the retrospective selection of the controls was not done in any way that would systematically reduce rates of any specific disease. Therefore, it is unclear which factors might give rise to such low leukaemia rates in the controls, other than perhaps chance.

Over the additional 19 years of follow-up since the last analysis, mortality from non-CLL leukaemia among test participants was similar to that expected from national rates and there was little evidence that the non-CLL mortality rate was higher than in the control group (RR 1.04, 90% CI 0.76–1.42, $p = 0.42$). However, during this period, for non-CLL incidence, there was a suggestion of a raised rate among test participants compared with controls (RR 1.32, 90% CI 0.99–1.78, $p = 0.06$). Among leukaemia sub-types, the evidence for a higher risk of both incidence and mortality among test participants compared with controls was greatest for CML(where a significant RR was observed) although RR estimates greater than unity were also observed for both AML and ALL. For CML there was also evidence to suggest that the incidence rate amongst the participants was above that expected based on national figures (SIR = 151, $p = 0.03$).

The increase in non-CLL risk (both mortality and incidence) seen in the earlier period (up to 1998) was driven by raised rates of myeloid leukaemia; AML and CML. While the evidence for a higher rate of AML in participants has disappeared with extended follow-up, the evidence for a raised rate of CML incidence has persisted through the latest follow-up period (SIR = 167, $p = 0.04$). Studies of the Japanese atomic bomb survivors and of some medically-exposed groups have shown that all three of these leukaemia sub-types (ALL, CML, AML) can be induced by radiation [34, 50, 51]. Recent pooled studies of large cohorts of nuclear workers [38, 39] have also shown evidence of potential persistent long-term effects of low dose radiation on non-CLL leukaemia risks, which was driven by larger increases for CML.

Although the relative difference between leukaemia rates in test participants and controls appears to have narrowed with increasing follow-up, there is still some evidence of a raised risk among participants relative

to controls, although this is mainly confined to CML. Given that mortality in controls is still low relative to national rates, the possibility of a chance finding cannot be ruled out. Nevertheless, the evidence for a raised risk appeared to be stronger when CML—which has been found to be radiation-inducible—was analysed separately.

There was no evidence of raised risks among men with a recorded dose, or of increasing risk with increasing dose among monitored test participants, although the numbers of cases in these analyses were limited. Among men who were in groups identified by MOD as liable to exposure to radiation or who were employed by AWE or who attended the minor trails at Maralinga or had a recorded dose greater than zero, leukaemia rates were not noticeably raised relative to national rates, nor was there clear evidence that risks relative to controls were higher among these men than among test participants overall, although the data were sparse.

Taken overall, the current analysis indicates that the possibility that test participation has caused a small increased risk of leukaemia other than CLL cannot be ruled out and that, whilst the evidence for any risk appears to have been greatest in the early years after the tests, a small risk might have persisted in more recent years, this long-term risk being particularly evident for CML.

4.5. Other cancers

There is evidence from epidemiological studies of the Japanese atomic bomb survivors and of patients who received high radiation doses, that radiation can induce a range of cancers [22, 36, 52, 53]. The evidence also suggests that cancer types vary in their sensitivity to induction from radiation exposure; the largest difference appears to arise between leukaemia and solid cancers generally, with smaller differences between different types of solid cancers [36, 54].

The interpretation of results for specific cancer types requires some care since, simply by chance, one would expect about one finding that is statistically significant at the 5% level for every 20 cancer types studied. Significant differences between the test participants and controls were observed for some individual cancer sites. Prostate (mortality only), stomach and bladder cancer were higher in the participants, while cancer of kidney was raised in the controls, but for none of these cancers were the rates in the participants raised relative to the national population over the whole follow-up period. Lung cancer mortality and incidence rates in the more recent period of follow-up (1999–2017), and the prostate cancer incidence rate in the earlier follow-up period (up to 1998), were significantly raised compared with the national population and the control group. For benign brain and CNS cancers, incidence among the participants was raised in both the earlier and later follow-up periods compared to the national population. Over the whole follow-up period there was also a significant excess incidence of these cancers among the participants relative to the controls, however in the latest follow-up period the evidence for an excess was weaker ($p = 0.07$).

4.6. Prostate cancer

For prostate cancer, there was some evidence that the mortality rate in participants was higher than in the controls (RR 1.16, 90% CI 1.03–1.30), but the incidence analysis showed no evidence of an overall difference (RR 1.01, 90% CI 0.95–1.07). This could suggest the raised mortality rate was a chance finding. However, there was evidence of a raised incidence rate in the participants relative to both the national population (SIR = 121, $p = 0.002$) and the control group (RR 1.18, 90% CI 1.02–1.35) in the period prior to 1999. While these early raised rates in the participants have fallen back to national levels in the most recent period of follow-up (SIR = 97), it should be remembered that the prevalence of prostate cancer in the UK has increased dramatically over recent time due to increased diagnostic testing, which may make it harder to detect any adverse effect associated with the tests. Alternatively, the raised risk of this disease among participants seen in the first 40 years of follow-up (SMR = 126, $p = 0.02$; SIR = 123, $p = 0.001$, tables S16(d) and (b)) and the risk comparable with national rates in the fifth and sixth decades of follow-up (SMR = 97, SIR = 97, tables S16(d) and (b)), could indicate a detriment associated with the tests which has fully expressed itself with the first 40 years of follow-up.

The raised incidence rate of prostate cancer was more evident among men who were in groups identified by MOD as most liable to exposure to radiation (SIR = 138, $p = 0.01$) or employed by AWE or who were directly involved in the minor trails at Maralinga (SIR = 131, $p = 0.01$) (table S8) and, therefore, most likely to be exposed to internal radionuclides. These rates were particularly raised among men identified as crew on HMS Diana (SIR = 180, $p = 0.003$) when it sailed through the fallout plume in Operation Mosaic (table S18(a)). Another potential explanation of this pattern of results is that the health monitoring of participants was greater than for controls (through self-selection or otherwise) and these differences disappeared as the prevalence of prostate cancer increased in the general population due to increased monitoring and better diagnosis. Other studies of US (SMR = 113, based on 1977 deaths) and Australian (SIR = 122, based on 548

cases) veterans [29, 48] involved in nuclear tests have also shown raised rates of prostate cancer in relation to the national population, although no increases in risk with estimated radiation dose were observed.

Until recently, neither the Japanese A-bomb survivor studies [55] or studies of nuclear workers [17, 56] suggest that the prostate is particularly radiosensitive. However, a more recent analysis of prostate cancer incidence in the bomb-survivors [57] has shown good evidence of a possible linear association between prostate cancer and radiation exposure that has only become apparent as survivors exposed as young adults or children have reached ages where the background level of prostate cancer risk is increased. Other smaller studies have suggested a possible link between prostate cancer and radiation exposure [58–60]. Several other risk factors are associated with prostate cancer such as age, ethnicity, family history, obesity and diet, but only age could be considered in the analysis as no information on the other factors was available. While these factors are unlikely to be very different between the participants and controls, the possibility of a small confounding effect from these factors cannot be ruled out.

4.7. Respiratory cancer

The raised rate of respiratory cancer incidence and mortality in the participants relative to the controls over the whole follow-up period reflect the results for lung cancer, where, during the most recent period of follow-up, raised rates were observed in participants (SMR = 110, $p = 0.02$; SIR = 111, $p = 0.004$), while the rates in the control group (SMR = 96, SIR = 102) were in line with the national rates. This finding is a reversal of the pattern in earlier analyses [4], which indicated that lung cancer rates were higher in the control group and provided no evidence for an excess of respiratory cancers among the participants relative to the controls.

Besides smoking, there are occupational exposures that are associated with increased risk of lung cancer including arsenic, chromium, nickel, asbestos, radon gas and radiation. The raised rates of pleural cancer in both participants (SIR = 130, $p = 0.007$) and controls (SIR = 139, $p < 0.001$) clearly suggest that both groups of veterans were occupationally exposed to asbestos. However, there was no evidence that pleural cancer rates in participants were higher than those in controls (RR = 0.97). Asbestos is known to be have been extensively used in naval vessels. An excess of mesothelioma was first observed among UK Navy servicemen who served abroad in the 1950's and 60's, but based on only a few cases [61]. This study was based on the combined cohort of test participants and controls included in this study, with follow-up truncated at the end of 1983, although AWE employees and servicemen with less five years-service were excluded. The study [61] coded mesothelioma directly from searches of deaths certificates, as it could not reliably be inferred from ICD codes prior to ICD-10. This fourth analysis of the test participants now uses ICD-10 codes from 1995 onwards and includes all mesotheliomas from this more recent period (1995 onwards), along with all pleural cancers from the earlier period (i.e. prior to 1995), in a combined grouping of pleural cancer and mesothelioma. For convenience, this grouping has simply been referred to as pleural cancer throughout the text and tables. The current study extends and confirms these earlier findings, with the excess of pleural cancer in participants still limited to naval personnel (SIR = 262, $p < 0.001$, based on 70 cases, table S12(b)). The US 'Eight series study' [29, 62] also found a significant excess of pleural cancer among sailors, but not among other servicemen (RR = 1.34. $p = 0.07$) and similar findings were observed among Australian veterans involved in the UK tests [48], where raised rates were restricted to naval personnel . These results suggest that asbestos exposure is unlikely to be the explanation for the raised lung cancer rates in recent years.

Raised lung cancer risk has been clearly linked to radiation exposure in the A-bomb survivor studies [55, 63] and there is evidence of a link from a pooled analysis of nuclear worker studies [17] exposed at much lower doses than the A-bomb survivors. There was very little evidence of increased rates among the participant sub-groups identified as most likely to be exposed or that risks increased with dose in the participants with measured doses, but the findings have low statistical power. While different temporal changes in smoking habits between the participant and control groups is a potential cause of the raised RRs for respiratory cancers seen in the most recent follow-up period, the results for other diseases related to smoking, such as IHD and COPD, do not support this interpretation. This suggests the impact of smoking habits on the overall pattern of results observed may be limited, but not open to simple interpretation.

4.8. Brain and CNS tumours

In groups identified by MOD as most liable to exposure to radiation, there was some evidence that rates of tumours of the brain and CNS were raised relative to national figures (SIR = 199, $p = 0.08$) and the controls (RR 1.94, 90% CI 1.07–3.50, $p = 0.04$, based on nine cases, table S8). Stronger evidence was observed for the group of participants most likely to have been exposed to internal radionuclides (i.e. participants at the Maralinga trials or AWE employees), with rates higher than both the national population (SIR = 217, $p = 0.01$) and the control group (RR 2.18, 90% CI 1.11–4.29, $p = 0.03$, based on 14 cases, table S8). It should

be noted that there is small overlap between these two subgroups (56 men) that account for two of these brain cancer and this should be borne in mind when trying to interpret the findings based on such as small number of events (further details on the special exposure groups can be found in the supplementary material). The number of participants and events in these subgroups is relatively small, 21 brain and CNS cases in both subgroups combined, and thus the statistical power to detect the cause of these effects is limited and the possibility that this is a chance finding cannot be excluded.

Both malignant and benign tumours were included in our analyses of tumours of brain and CNS, but separate analyses of the malignant and benign tumours revealed that the excess of cases was most marked for benign (SIR = 360, $p = 0.01$, based on 6 cases) rather than malignant tumours (SIR = 167, $p = 0.08$, based on 15 cases, results not presented in tables). This pattern of higher rates of benign brain tumour incidence was also clear in the whole cohort of test participants, where rates were higher than the national population (SIR = 208, $p < 0.001$, based on 43 cases) and the control group (RR 1.97, 90% CI 1.29–3.02, $p = 0.004$). Among these 43 cases, only 13 had a measured dose, of which six were zero, and there was no evidence of a difference in risk between those with a positive and zero recorded dose (RR 1.83, 90% CI 0.64–5.23, $p = 0.17$), despite rates being significantly raised in those with positive dose when compared with the national population (SIR = 423, $p = 0.00$, based on seven cases, table S6). Although these few cases provided no evidence for a dose response relationship, a significant dose–response relationship has been reported in many cohorts of patients receiving radiotherapy for either benign or malignant diseases [36]. The most recent study of CNS tumours in the A-bomb survivors [55] also showed raised rates, particularly for non-malignant tumours. These studies also found some evidence that increases tend to be greatest for individuals exposed at younger ages and that risks decline with attained age. So overall, while the measured doses in the test participants appear to be too low to induce CNS tumours, there are some aspects of results (increased rates in subgroups identified as being most exposed) that could point towards radiation exposure playing a role in the increased risks. However, exposures to various chemicals have been linked to CNS tumours and, given the low measured radiation doses in this study, there is insufficient information to make any firm conclusion about the most likely cause of the benign tumour excess.

4.9. Bladder cancer

For bladder cancer, there was some evidence that both mortality and incidence rates in participants were higher than in the controls (RR 1.17, 90% CI 0.96–1.41 $p = 0.09$, mortality; RR 1.14, 90% CI 1.01–1.27 $p = 0.03$, incidence), but no evidence that they were raised compared to national rates for either mortality (SMR = 93, $p = 0.40$) or incidence (SIR = 102, $p > 0.5$). The excess appeared to be mainly driven by lower rates in the control group (SMR = 81, $p = 0.009$ and SIR = 91, $p = 0.07$) and this was particularly evident in the period up to 1998 where the bladder cancer mortality rate for the controls was very low (SMR = 56, $p < 0.001$). Studies of the A-bomb survivors have reported strong associations between radiation dose and bladder cancer, with the excess risk amongst the highest reported for any cancer site [55]. Other risk factors for bladder cancer have been identified, including smoking and occupational exposure to aromatic amines [64], and differences in exposure to these factors between groups could be a potential explanation for the pattern of results, although no additional information on these factors was available for analysis. In this study, the increased RRs may well simply be a chance finding especially as there is little evidence that bladder cancer risk was elevated in groups identified as most likely to have been exposed to radiation.

4.10. Stomach cancer

Both stomach cancer mortality and incidence showed evidence of raised rates in participants relative to controls (RR 1.16, 90% CI 1.00–1.35 $p = 0.05$, incidence; RR 1.20, 90% CI 1.00–1.43 $p = 0.05$, mortality), however in both cases this appeared to be driven by lower rates in the controls (SIR = 75, $p < 0.001$; SMR = 68, $p < 0.001$) rather than high rates in the participants (SIR = 88, $p = 0.04$; SMR = 82, $p = 0.005$). The overall raised RR estimate (RR = 1.16) for all participants was mainly driven by officers (RR 2.55, 90% CI 1.57–4.14 $p < 0.001$, table S14(a)) rather than other ranks (RR 1.06, 90% CI 0.90–1.24 $p = 0.28$), although this elevated RR was attributable to very low rates in the officer controls (SMR = 25, $p < 0.001$, table S14(b)) rather than high rates in participant officers (SMR = 61, $p = 0.002$). There was also no evidence that stomach cancer rates were raised in subgroups identified as most likely to have been exposed or that risks increased with level of recorded radiation dose. While stomach cancer rates have been found to be associated with radiation exposure in various studies [55, 65], it is likely, given the low rate of stomach cancers in the participants and the absence of raised rates in any of the groups identified as most likely to have been exposed, that the observed raised risks are due to chance rather than any adverse effect associated with the tests.

4.11. Other sites

The only cancer site to show lowered rates in participants relative to controls was cancer of the kidney and ureter (for both incidence and mortality). This finding was based on significantly higher rates in the control group (SIR = 126, $p < 0.001$; SMR = 125, $p = 0.01$) rather than lower rates in the participants (SIR = 104, $p > 0.5$; SMR = 102, $p > 0.5$). As mentioned above, because of multiple hypothesis testing associated with many disease endpoints, this could well be a chance finding.

Two of the few cancer sites that show increased incidence rates in participants when compared with the national population are NMSC (SIR = 121, $p < 0.001$) and malignant melanoma (SIR = 128, $p < 0.001$). However, rates in the control group were also similarly raised and there was no evidence that rates differed between the groups (RR = 0.98, $p = 0.21$ for NMSC; RR = 1.05, $p = 0.30$ for malignant melanoma). The main cause for both diseases is exposure to ultra-violet (UV) radiation and one of criteria for selecting the control group was that they had served in tropical areas overseas while in the services, where UV exposure was likely to have been high. Thus, UV radiation is very likely to be the cause of the increased rates in both groups.

The only other cancer sites (not mentioned above) to show raised incidence or mortality in the participants relative to the national population were cancer of the mouth and pharynx (SIR = 127, $p = 0.02$; SMR = 133, $p = 0.046$). Rates in the control group were also similarly raised (SIR = 140, $p < 0.001$; SMR = 147, $p = 0.004$) and there was no evidence that rates were different between the two groups for either mortality (RR 0.92, 90% CI 0.68–1.24) or incidence (RR 0.93, 90% CI 0.75–1.16). Mouth cancers have several suspected causes, including tobacco use of any kind (cigarettes, cigars, pipes, chewing tobacco and snuff etc) and excessive use of alcohol [66]. It may be significant that, among non-cancer diseases, the only outcome to show elevated risks relative to the national population in either participant or control group was cirrhosis of the liver (SMR = 128, $p < 0.005$ for participants; SMR = 148, $p < 0.001$ for controls). This result may indicate that alcohol use in certain subgroups of veterans was somewhat higher than in the general population (e.g. cirrhosis SMR of 219, $p < 0.001$, for Royal Navy participants, table S13) and this may well be a partial explanation of the higher rates of cancer of the buccal cavity and pharynx (SIR of 147, $p = 0.007$, for Royal Navy participants, table S12). Given the above results, it would seem likely that any increases in mouth cancers among participants are related to the factors mentioned rather than involvement in the tests.

In the previous analysis of the cohort [10], liver cancer incidence was noted to show raised rates in participants relative to controls (RR 2.03, 90% CI 1.21–3.43, based on 33 cases), although evidence of an effect was limited by the absence of an effect for mortality and the authors were equivocal about whether this finding may be due to chance or not. The current analysis, with extended follow-up, shows no evidence of raised rates of liver cancer incidence (RR 1.09, 90% CI 0.91–1.32, based on 154 cases) or mortality (RR 1.03, 90% CI 0.81–1.30, based on 95 deaths), in participants relative to controls, indicating that the earlier finding is likely to have been indeed been a chance finding.

4.12. Non-cancers

At the time of the last analysis most of the evidence relating radiation to health effects occurring years or decades subsequently concerned the induction of cancer. However, in recent years, further follow-up of the Japanese atomic bomb survivors and other populations has also pointed to raised risks of mortality from non-cancer diseases [67, 68] and in particular circulatory diseases [68–70]. Whilst the evidence for such an effect is strongest at doses more than 0.5 Sv, there is now some evidence that excess risk might extend down to low doses [71]. As a result, in this analysis we have examined non-cancer outcomes in greater detail.

Apart from cirrhosis of the liver (mentioned above), mortality rates in both test participants and controls were generally lower than the national population, most likely because of the long-term impact of the HSE (mentioned earlier). There is some limited evidence that overall non-cancer disease mortality was slightly higher in participants than controls (RR = 1.02, 90% CI 1.00–1.05, $p = 0.07$). This was driven by higher rates of cerebrovascular disease (RR = 1.12, 90% CI 1.03–1.21, $p = 0.01$) in participants relative to controls, although the rate among participants was still low relative to the national population (SMR = 91, $p = 0.004$). For cerebrovascular disease the evidence was driven by elevated risk during most recent period of follow-up period, 1999–2017 (RR = 1.18, 90% CI 1.06–1.31), with little evidence of an effect when restricting follow-up to 1998 (RR = 1.03, 90% CI 0.90–1.17). There was also some evidence that cerebrovascular disease rates were increased, relative to controls, in groups previously identified by MOD as most liable to exposure i.e. RRs of 1.24 and 1.28 for special exposure groups A and B respectively.

A-bomb survivor studies show some evidence that cerebrovascular disease risks are associated with external radiation dose [68], although risks appear higher for other circulatory diseases and in particular, heart disease. There is also some evidence that low doses of radiation may be associated with increases in cerebrovascular diseases [71, 72]. For example, a pooled study of 300 000 nuclear workers from France, USA and UK observed a significant increase in cerebrovascular disease risk down to 100 mSv [69], but a biological

mechanism for these effects is unclear and the idea that low doses of radiation can cause increases in non-cancer disease risk remains controversial.

Cerebrovascular diseases have several established risk factors including smoking, diabetes, obesity, hypertension and high levels of blood cholesterol [71, 72]. In the absence of information on these risk factors, the current study has attempted to partially control for some of them through adjustment for rank and service in the analysis. However, by their very nature, surrogate measurements for these risk factors are not as good as actual measurements and some residual confounding may partially explain the pattern of results observed. As discussed earlier, there are some indications (from the lung cancer results) that smoking rates in the controls may have declined faster than in participants in recent years. However, if smoking was the cause of the raised cerebrovascular disease risks then it would be reasonable to see a similar pattern of results for IHD and COPD, which are just as strongly related to smoking, but, this is not the case, with no evidence of increased risk in participants for these diseases. This analysis cannot rule out the possibility that some long-term risk of cerebrovascular disease is associated with the test participation and, without further information on the major risk factors for cerebrovascular disease, this study cannot be more definitive in this area.

In the period included in the last analysis, up to 1998, mortality from all accidents and violence was similar among test participants and controls, although the rates for both groups were raised relative to national rates levels (SMRs of 121 and 115). The increased risks have declined, when including the last 19 years of follow-up, to the point where rates are no longer significantly elevated in the controls (SMR = 105, $p = 0.24$) and are less elevated in the participants (SMR = 111, $p = 0.01$). The increased rate of accidents and violence in the participants is driven by deaths associated with accidents (SMR = 113, $p = 0.02$) and acts of intentional self-harm (SMR = 130, $p = 0.005$). Although raised rates of deaths associated with accidents (SMR = 109, $p = 0.12$) and acts of intentional self-harm (SMR = 114, $p = 0.19$) were also observed in the control group, there was no evidence they were raised in comparison with national levels. The highest rates for acts of intentional self-harm were seen in the first ten years of follow-up for both the participants (SMR = 854, $p < 0.001$, 18 deaths, table S17(b)) and control groups (SMR = 331, $p < 0.001$, 20 deaths, table S17(c)). A study of UK Gulf War veterans found evidence of a raised risk of mortality from accidents and violence, relative to a matched control group [73] and suggested it might reflect differences between Gulf War veterans and controls in their perception of risk or in activities that they undertook subsequently. However, the period following operations covered by this Gulf War study (less than ten years follow-up) is much shorter than the follow-up in the current study and longer follow-up of the UK gulf war veterans cohort have shown decreased rates of accidents in comparison with the national population [74].

5. Conclusions

This fourth analysis of men from the UK who participated in the UK nuclear weapon tests programme has continued to show that overall levels of mortality are lower than expected from national rates, although this difference has narrowed with longer follow-up. The results do, however, show some evidence that overall mortality in participants may be marginally higher than in the control group, although the size of the difference is small (2%) and has only emerged with extended follow-up as the power to detect small differences in risk between the groups has accumulated. Given the small size of the difference, it is entirely possible that heterogeneity in the background characteristics that could not be accounted for in the analysis (e.g. smoking habits, diet), between participants and the control group, could be responsible. However, the possibility that there is some small long-term detrimental health effect associated with participation in the tests cannot be completely ruled out.

The analysis provides further evidence that the increased multiple myeloma risks noted in the first analysis are no longer present with extended follow-up and reinforces the conclusion that the earlier result is likely to have been a chance finding. For leukaemia, the evidence of increases in risk among participants in the early years after the tests has continued to diminish with time, although there is still evidence that non-CLL risks are higher in participants than the matched control group. This evidence is particularly strong for CML, where increase in risk has persisted over time to the extent where the incidence rate is now raised in comparison with both the national population and the control group. There was some evidence of increased rates in participants relative to controls for cancers of the stomach, bladder and respiratory system, however the interpretation of these findings is difficult given the lack of potential confounding information and lack of raised risks in sub-groups identified as most likely to be exposed.

For the first time, there was some evidence that participants had higher mortality rates from cerebrovascular diseases than did the controls and this was particularly clear in the additional follow-up period. It may be significant that for both CML and cerebrovascular diseases, associations have been observed between long-term disease rates and chronic low doses of radiation in large pooled nuclear workers

studies. However, it should be stressed that if the recorded radiation exposures in the participants, which are generally very low, are a true reflection of actual exposures, then it is unlikely that any observed health effect will have been caused by their radiation exposure. Analysis of subgroups identified as having greater potential for exposure provided some evidence of raised rates of brain and prostate cancers in participants, with little evidence for other diseases. However, the number of men involved in such comparisons was limited and the possibility that these are chance findings cannot be ruled out.

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