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Cancer morbidity in British military veterans included in chemical warfare agent experiments at Porton Down: cohort study

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ABSTRACT

Objective To determine cancer morbidity in members of the armed forces who took part in tests of chemical warfare agents from 1941 to 1989.

Design Historical cohort study, with cohort members followed up to December 2004.

Data source Archive of UK government research facility at Porton Down, UK military personnel records, and national death and cancer records.

Participants All veterans included in the cohort study of mortality, excluding those known to have died or been lost to follow-up before 1 January 1971 when the UK cancer registration system commenced. 17 013 male members of the UK armed forces who took part in tests (Porton Down veterans) and a similar group of 16 520 who did not (non-Porton Down veterans).

Main outcome measures Cancer morbidity in each group of veterans; rate ratios, with 95% confidence intervals, adjusted for age group and calendar period.

Results 3457 cancers were reported in the Porton Down veterans compared with 3380 cancers in the non-Porton Down veterans. While overall cancer morbidity was the same in both groups (rate ratio 1.00, 95% confidence interval 0.95 to 1.05), Porton Down veterans had higher rates of ill defined malignant neoplasms (1.12, 1.02 to 1.22), in situ neoplasms (1.45, 1.06 to 2.00), and those of uncertain or unknown behaviour (1.32, 1.01 to 1.73).

Conclusion Overall cancer morbidity in Porton Down veterans was no different from that in non-Porton Down veterans.

INTRODUCTION

After the first world war, research conducted at the chemical defence establishment at Porton Down included a “human volunteer programme” and members of the armed forces took part in experiments studying the potential impact of chemical agents on military capability and the effectiveness of protective measures.^{1,2} Between 1941 and 1989, over 18 000

members of the armed forces were recorded as having taken part in this programme. Over 50% of these veterans were recorded as taking part in tests involving chemicals that are known or probable human carcinogens, the most common being dermal exposures to sulphur mustard.³ While their overall cancer mortality was similar to that of veterans who did not take part in tests at Porton Down,⁴ past exposure to these chemicals might have affected their risk of developing common cancers with relatively good survival such as certain skin cancers. We report here on cancer morbidity in Porton Down veterans by studying cancers reported for the period from 1971, when the UK cancer registration system commenced, to 2004.

METHODS

Information provided here focuses on aspects relevant to cancer morbidity. More details of the methods used are provided elsewhere.⁴

Study population

We considered for inclusion all veterans included in the cohort study of mortality.⁴ Porton Down veterans were all male members of the British armed forces recorded as having participated in tests between 1 April 1941 and 31 December 1989, while non-Porton Down veterans were other similar members of the armed forces not recorded as having taken part in tests at Porton Down.⁴ We excluded veterans known to have died or been lost to follow-up before 1 January 1971.

Follow-up

We obtained death certificates, notifications of emigrations, and data on cancers registered since 1 January 1971 from the National Health Service central registers.⁴ Each condition listed on death certificates as causing or contributing to death was coded by the Office for National Statistics according to ICD-10 (international classification of diseases, 10th revision). Cancer registration data for all cancers registered on or

after 1 January 1971 were provided electronically and included date of diagnosis and cancer site or type coded according to the ICD coding system at the time of registration (ICD-8, 9, or 10). The research team recoded ICD-8 and ICD-9 codes to ICD-10 codes.

Classification of chemical exposures

We used contemporaneous experimental records of tests carried out as part of the “human volunteer programme” in the Porton Down historical archive to retrospectively assess exposure.^{3,5} Data abstraction

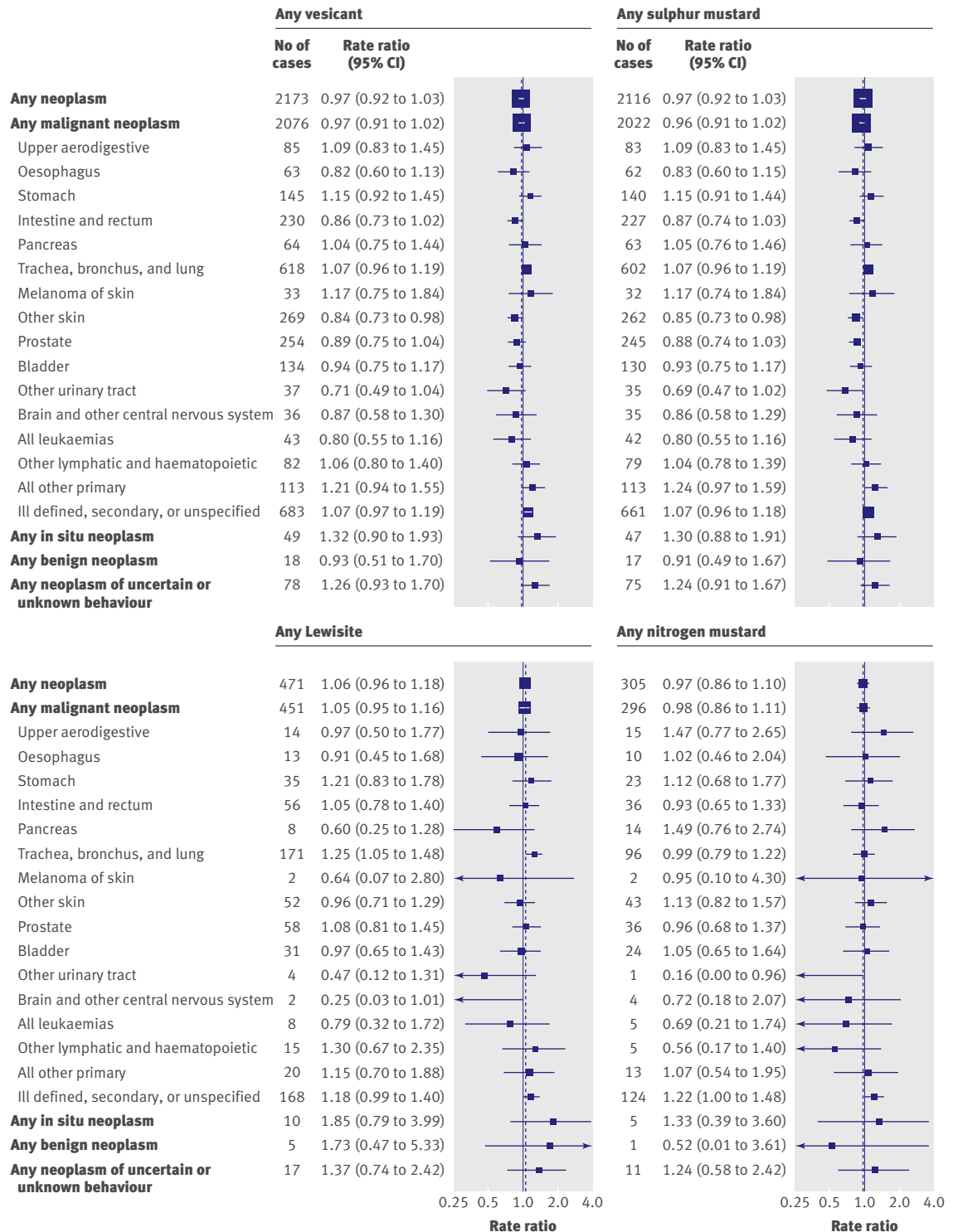


Fig 1 | Rate ratios for selected cancer sites or types in Porton Down veterans included in tests involving vesicants relative to all non-Porton Down veterans, adjusted for age group and calendar period. Rate ratio estimates are represented by box with size inversely proportional to variance. Vertical dotted line shows the estimate for any neoplasm

involved linking, when possible, each test to an individual veteran and the classification of that test as involving a chemical or not. The type of chemical was recorded as being a vesicant (blistering agent), a nerve agent, or other chemical. There were eight specific chemicals for which there were records of at least 1000 Porton Down veterans having been tested: three vesicants (sulphur mustard, Lewisite, and nitrogen mustard), one nerve agent (sarin), two lachrymators (CS and CR), and two anti-nerve agent pharmaceutical chemicals (pralidoxime and atropine). Two of these

Table 1 | Characteristics of 17 013 Porton Down veterans and 16 520 non-Porton Down veterans contributing to cancer morbidity analyses. Figures are numbers (percentages) of veterans

Characteristic	Porton Down veterans	Non-Porton Down veterans
Service at enlistment:		
Army	10 348 (60.8)	9976 (60.4)
Air force	3924 (23.1)	3885 (23.5)
Navy (and marines)	2741 (16.1)	2659 (16.1)
Decade of birth:		
Before 1920	2988 (17.6)	3125 (18.9)
1920s	3168 (18.6)	2960 (17.9)
1930s	5942 (34.9)	5833 (35.3)
1940s or later	4915 (28.9)	4602 (27.9)
Place of birth:		
England	13 440 (79.9)	12974 (79.2)
Wales	846 (5.0)	861 (5.3)
Scotland	1607 (9.6)	1673 (10.2)
Other	908 (5.4)	864 (5.3)
Age (years) at enlistment:		
<16	1207 (7.1)	1192 (7.2)
16-<18	4831 (28.6)	4178 (25.3)
18-<20	6104 (36.1)	5896 (35.7)
20-<22	2081 (12.3)	2242 (13.6)
≥22	2688 (15.9)	3002 (18.2)
Period at enlistment*:		
Before second world war	749 (4.4)	706 (4.3)
During second world war	4448 (26.3)	4347 (26.3)
After second world war	7571 (44.8)	7462 (45.2)
After national service	4143 (24.5)	3995 (24.2)
Total duration of service†:		
<2	397 (2.4)	2705 (16.4)
2-<3	2761 (16.5)	3304 (20.0)
3-<4	2499 (14.9)	2480 (15.0)
5-<10	6355 (37.9)	5040 (30.5)
≥10	4755 (28.4)	2980 (18.1)
Vital state at 31 December 2004:		
Alive	10 396 (61.1)	10 222 (61.9)
Deceased	6510 (38.3)	6197 (37.5)
Follow-up censored at:		
Discharge from services	41 (0.2)	30 (0.2)
Emigration	17 (0.1)	20 (0.1)
Other	49 (0.3)	51 (0.3)

*Second world war dates taken as 1 September 1939 to 30 April 1945; national service dates taken as 1 May 1945 to 31 December 1960.

†Includes 148 Porton Down veterans, and 132 non-Porton Down veterans still serving at time of data abstraction.

Table 2 | Exposure data abstracted in 17 013 Porton Down veterans contributing to cancer morbidity analyses

	No (%) of veterans
No of tests:	
1	2010 (11.8)
2-5	3844 (22.6)
6-9	3523 (20.7)
10-14	2806 (16.5)
≥15	3910 (23.0)
None	920 (5.4)
Decade of first test*:	
1940s	5437 (32.0)
1950s	5933 (34.9)
1960s	2230 (13.1)
1970s	1964 (11.5)
1980s	1449 (8.5)
No of chemical tests‡:	
≥1	15 481 (96.2)
None	612 (3.8)
Type of chemical test‡:	
Vesicant:	
Any	9473 (58.9)
Sulphur mustard‡	9232 (57.4)
Lewisite	1437 (8.9)
Nitrogen mustard	971 (6.0)
Nerve agent:	
Any	3488 (21.7)
Sarin	2896 (18.0)
Other chemical:	
Any	11 292 (70.2)
CS	1315 (8.2)
CR	1172 (7.3)
Pralidoxime	1690 (10.5)
Atropine	1552 (9.6)
Benzene	812 (5.0)

*Date of first visit for those with no test data.

†Includes 16 039 veterans for whom type of test could be determined.

‡Includes mustard sensitivity tests.

chemicals have been classified by the International Agency for Research on Cancer (IARC) as either a known (sulphur mustard and cancer of the upper and lower respiratory tract) or probable (nitrogen mustard and squamous cell carcinoma of the skin) human carcinogen.⁶ We also considered benzene, a chemical classified by IARC as a leukaemogen⁶ and used as a diluent in tests in 994 veterans.³

Of the veterans recorded as being exposed to sulphur mustard, 74% of those in the analyses of cancer morbidity could be classified according to cumulative exposure. Veterans exposed to a total of ≥10.63 mg of sulphur mustard were classified as having “high” exposures.³ Equivalent classifications were possible for 66% of veterans exposed to Lewisite and 75% of those exposed to nitrogen mustard, the corresponding “high” exposure levels being ≥13.69 mg and ≥23.73 mg, respectively.³ For 93% of tests involving sulphur mustard, we could classify veterans according to the biological effect recorded, equivalent figures

being 98% for Lewisite and 83% for nitrogen mustard. Veterans with a least one dermal vesicle or a necrosed area recorded after tests involving these vesicants were classified as having had an exposure with at least one “high” biological effect. The derivation of these groups, and of similar groups for nerve agent exposures, is described elsewhere.³ For chemicals other than vesicants or nerve agents, we collected information on the number of tests recorded.

Statistical analysis

All veterans included in the previously reported mortality analysis as alive and under follow-up on or after 1 January 1971 contributed to the analysis. The primary method involved comparing registration rates in Porton Down veterans with those of non-Porton Down veterans by calculating rate ratios. For each Porton Down veteran, we counted person years of follow-up from 1 January 1971 or the earliest subsequent date that they were first recorded as being included in a test. For non-Porton Down veterans, we counted person years from the date derived by adding to their enlistment date the time between enlistment and first attendance at Porton Down for the veteran for whom they had been selected. For each specific cancer site or type, person years stopped at the earliest of date of registration of the first cancer, death, loss to follow-up, or 31 December 2004. For veterans lost to follow-up, person years stopped at the last date they were

known to be alive (such as date of emigration or discharge from the services). When we compared rates in Porton Down and non-Porton Down veterans we included cancers identified only from the death certificate. For cancers identified in this way, we used the date of death as the date of cancer registration.

Rate ratios were estimated for all neoplasms combined and according to type (malignant, in situ, benign, uncertain or unknown behaviour). For malignant neoplasms, we also estimated rate ratios separately for 16 predetermined cancer sites or types. Veterans with more than one cancer of the same site or type had only the first cancer counted while those with cancers registered for two or more different types (such as primary cancers of skin and bladder) contributed a cancer to each. We calculated person years separately for each cancer site or type stratified according to 15 five year age groups (15-19, 20-25, etc, to ≥85) and five year calendar periods (1971-4, 1975-9, etc, to 2000-4). All rate ratios were adjusted for age group and calendar period and estimated with 95% confidence intervals, and P values calculated, with the Mantel-Haenszel method.⁷ When the number of cancers expected in either group of veterans was less than 10, we estimated adjusted rate ratios and tested for significance by fitting exact conditional Poisson regression models to the stratified data.⁸

We also compared rates of cancer in each group of veterans with rates in England and Wales, using only

Table 3 | Rate ratios (95% confidence intervals) for selected cancer sites and types in Porton Down veterans relative to non-Porton Down veterans, unadjusted and adjusted for age group and calendar period

Cancer site/type (ICD-10 code)	No of cases		Rate ratio	
	Porton Down veterans	Non-Porton Down veterans	Unadjusted	Adjusted (95%CI)
Any malignant neoplasm (C00-C97)	3114	3140	0.96	0.99 (0.94 to 1.04)
Upper aerodigestive (C00-C14, C30-C32)	132	117	1.10	1.11 (0.87 to 1.43)
Oesophagus (C15)	103	115	0.87	0.89 (0.68 to 1.16)
Stomach (C16)	189	170	1.08	1.12 (0.91 to 1.38)
Intestine and rectum (C17-C20)	364	392	0.90	0.93 (0.81 to 1.07)
Pancreas (C25)	89	91	0.95	0.98 (0.73 to 1.31)
Trachea, bronchus, and lung (C33, C34)	851	782	1.06	1.09 (0.99 to 1.20)
Melanoma of skin (C43)	60	50	1.17	1.19 (0.82 to 1.74)
Other skin (C44)	436	496	0.86	0.87* (0.77 to 0.99)
Prostate (C61)	381	422	0.88	0.92 (0.80 to 1.05)
Bladder (C67)	193	202	0.93	0.97 (0.79 to 1.18)
Other urinary tract (C64-C66, C68)	65	85	0.75	0.76 (0.55 to 1.04)
Brain and other central nervous system (C71, C72)	56	66	0.83	0.83 (0.58 to 1.19)
All leukaemias (C91-C95)	74	84	0.86	0.89 (0.65 to 1.21)
Other lymphatic and haematopoietic (C81-C90, C96)	139	126	1.08	1.09 (0.86 to 1.39)
All other primary malignant neoplasms†	182	148	1.20	1.22 (0.99 to 1.52)
Ill defined, secondary, or unspecified malignant neoplasms (C76-C80)	975	878	1.08	1.12* (1.02 to 1.22)
Any in situ neoplasm (D00-D09)	93	64	1.42	1.45* (1.06 to 2.00)
Any benign neoplasm (D10-D36)	31	31	0.98	0.99 (0.60 to 1.63)
Any neoplasm of uncertain or unknown behaviour (D37-D48)	126	95	1.29	1.32* (1.01 to 1.73)
Any neoplasm (C00-C97, D00-D48)	3288	3282‡	0.97	1.00 (0.95 to 1.05)

*P<0.05.

†C21-24, C26-C29, C37-C41, C45-C50, C60, C62, C63, C69, C70, C73-C75, C97.

‡Excludes neoplasms for four veterans for whom person years could not be calculated.

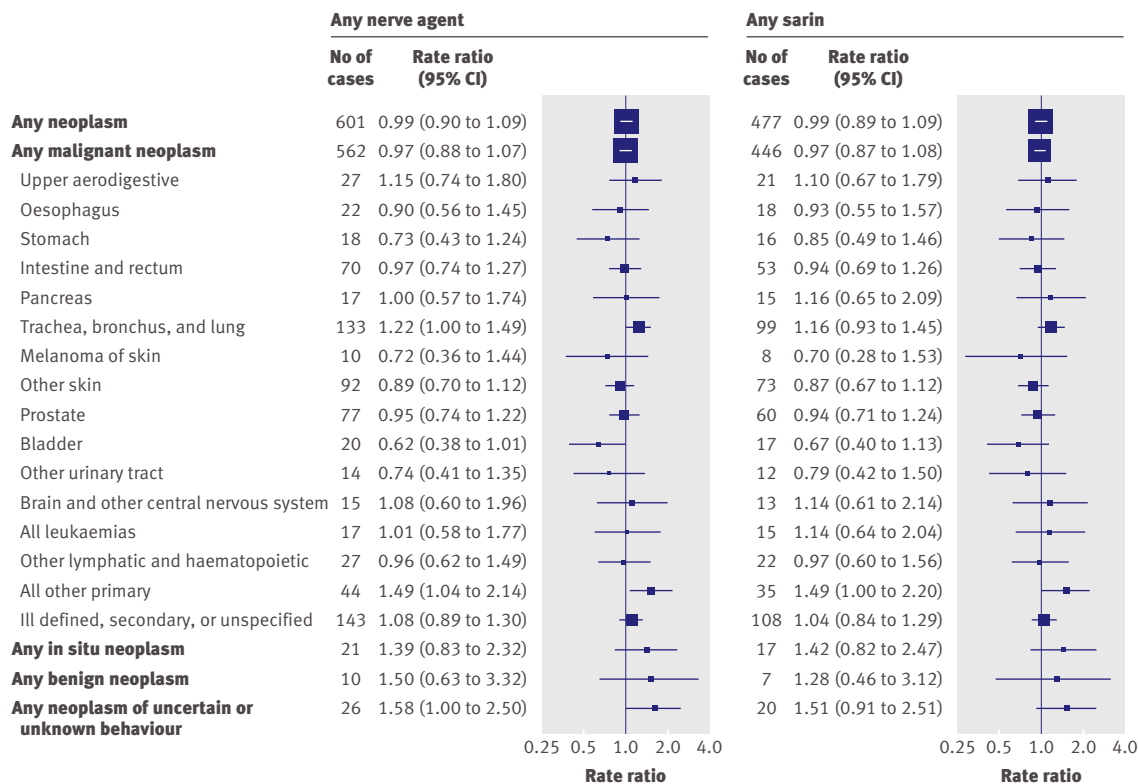


Fig 2 | Rate ratios for selected cancer sites or types in Porton Down veterans included in tests involving nerve agents relative to all non-Porton Down veterans, adjusted for age group and calendar period. Rate ratio estimates are represented by box with size inversely proportional to variance. Vertical dotted line shows the estimate for any neoplasm

those cancers notified from registrations. We counted person years from the same date as that used for rate ratio calculations but stopped at the date when the veteran was last known to be alive in the UK. We stratified person years of follow-up according to 15 five year age groups (15-19, 20-24, etc, to ≥ 85) and by single calendar year (from 1941 to 2004). Expected registrations were calculated by multiplying the person years for each five year age group and single calendar year by the corresponding registration rates for England and Wales. Standardised registration ratios were estimated from the ratio of observed to expected registrations. We obtained 95% confidence intervals and P values using the normal approximation to the Poisson distribution.⁸

Analyses reported here relate to 17 013 Porton Down veterans, and 16 520 non-Porton Down veterans, all of whom were included in mortality analyses.⁴ Updating of databases after the mortality analysis removed two Porton Down veterans and four non-Porton Down veterans from the analysis but added three non-Porton Down veterans. All analyses were performed with Stata 10 (www.stata.com). All tests of significance were two sided.

RESULTS

Of the veterans included in the mortality analysis, 93% (17 013/18 276) of Porton Down veterans and 94% (16 520/17 600) of non-Porton Down veterans

contributed data to analyses on cancer morbidity. Of those excluded from analyses, in over 60% of Porton Down (796/1263) and non-Porton Down veterans (703/1,080) this was because they had died between 1941 and 1970. Service at enlistment and other characteristics were similar to that of non-Porton Down veterans (table 1). As in the mortality study, Porton Down veterans had a longer total duration of military service. The distribution of Porton Down veterans according to frequency, calendar period, and type of chemical test was also similar to that reported previously (table 2).

The number of men with one or more cancer registrations was 3029 in Porton Down veterans and 3015 in non-Porton Down veterans. We identified a further 530 veterans with cancer from death certificates (259 and 271). The total number of cancers recorded in each group was 3457 and 3380, respectively. The percentage with two or more registrations was slightly larger in Porton Down than non-Porton Down veterans: 12.3% (374/3029) *v* 10.6% (320/3015).

Overall, rates for all neoplasms were the same in both groups of veterans (rate ratio 1.00, 95% confidence interval 0.95 to 1.05) as were those for all malignant neoplasms (0.99, 0.94 to 1.04) (table 3). Porton Down veterans had higher rates of ill defined, secondary, or unspecified malignant neoplasms (1.12, 1.02 to 1.22), in situ neoplasms (1.45, 1.06 to 2.00), and those of uncertain or unknown behaviour (1.32, 1.01 to 1.73)

Table 4 | Rate ratios (95% confidence intervals) for selected cancer sites/types (ICD-10) for Porton Down veterans with high recorded levels of exposure to specific chemicals relative to non-Porton Down veterans, adjusted for age group and calendar period

Chemical and indicator of high exposure level	No of cases	Adjusted rate ratio (95% CI)
Sulphur mustard		
Dermal ≥ 10.63 mg:		
Upper aerodigestive (C00-C14, C30-C32)	26	0.91 (0.60 to 1.40)
Trachea, bronchus, and lung (C33, C34)	207	0.98 (0.84 to 1.15)
Dermal vesicle:		
Upper aerodigestive (C00-C14, C30-C32)	38	1.28 (0.88 to 1.86)
Trachea, bronchus, and lung (C33, C34)	266	1.10 (0.95 to 1.27)
Lewisite		
Dermal ≥ 13.69 mg:		
Trachea, bronchus, and lung (C33, C34)	31	1.22 (0.85 to 1.75)
Other skin (C44)	11	1.17 (0.58 to 1.94)
Dermal vesicle:		
Trachea, bronchus, and lung (C33, C34)	76	1.26 (0.99 to 1.59)
Other skin (C44)	21	0.85 (0.55 to 1.33)
Nitrogen mustard		
Dermal ≥ 23.73 mg:		
Other skin (C44)	17	1.59 (0.97 to 2.61)
All leukaemias (C91-C95)	1	0.47 (0.01 to 2.78)
Dermal vesicle:		
Other skin (C44)	12	1.05 (0.59 to 1.87)
All leukaemias (C91-C95)	0	0.00 (0.00 to 1.74)
CS (two or more tests)		
Oesophagus (C15)	5	2.73 (0.84 to 6.97)
Pralidoxime (two or more tests)		
All neoplasms of uncertain or unknown behaviour (D37-D48)	5	2.88 (0.80 to 8.42)
Atropine (two or more tests)		
All neoplasms of uncertain or unknown behaviour (D37-D48)	3	2.28 (0.45 to 7.26)
Benzene (two or more tests)		
All leukaemias (C91-C95)	7	1.44 (0.55 to 3.21)

and lower rates of skin cancer other than melanoma (0.87, 0.77 to 0.99). Some neoplasms classified as in situ or of uncertain or unknown behaviour (16 in Porton Down and 10 in non-Porton Down veterans) were non-melanoma skin cancers. When we combined these with malignant skin cancers other than melanoma, the rate ratio for this cancer site increased only slightly (0.89, 0.78 to 1.01).

Rate ratios for all neoplasms and all malignant neoplasms were just below unity for veterans exposed to tests involving any vesicant, sulphur mustard, or nitrogen mustard and just above unity for Lewisite (fig 1). Veterans exposed to Lewisite had rates of cancer of the trachea, bronchus, and lung 25% higher than non-Porton Down veterans (1.25, 1.05 to 1.48, $P=0.01$). Porton Down veterans exposed to tests involving any nerve agent, sarin, or any chemical other than nerve agents or vesicants had rate ratios for all neoplasms and all malignant neoplasms just below unity (figs 2 and 3). The rate of cancer of the oesophagus was raised in veterans exposed to CS (2.17, 1.04 to 4.52, $P=0.03$).

Table 4 shows results for veterans classified as having had high levels of exposure or biological effect either for

chemicals with previous evidence of carcinogenicity (such as sulphur mustard for cancers of the trachea, bronchus, and lung) or where rate ratios were raised in Porton Down veterans (such as for CS and oesophageal cancer). When we compared the resultant estimates of rate ratios to the results for all exposed Porton Down veterans, in nearly all cases the estimate obtained was lower or similar to that obtained for all veterans. The only instance where the estimate for the high exposure group was above the upper limit of the 95% confidence interval for all veterans was for skin cancers other than melanoma in relation to high dermal exposure to nitrogen mustard (1.59, 0.97 to 2.61, v 1.13, 0.82 to 1.57). For veterans with a dermal vesicle recorded (high biological effect), however, the rate ratio estimate was lower than that of all exposed veterans (1.05, 0.59 to 1.87).

When compared with cancer registration rates in England and Wales, rates in Porton Down veterans were 10% lower for all neoplasms (standardised registration ratio 0.90, 0.87 to 0.93) and 6% lower for all malignant neoplasms (0.94, 0.91 to 0.98). Corresponding results for non-Porton Down veterans were 0.87 (0.85 to 0.90) and 0.94 (0.90 to 0.97), respectively.

DISCUSSION

Overall occurrence of cancer in veterans who took part in tests at Porton Down was similar to that of other veterans and lower than in the general population. These findings are in accord with their cancer mortality.⁴ We also found no evidence of an excess of any specific, clearly defined, cancer type or site in all Porton Down veterans combined. As expected, the similarity to our findings for mortality was particularly notable for highly fatal cancers such as those of the trachea, bronchus, and lung: the 9% higher rates of lung cancer morbidity in Porton Down veterans is identical to the excess reported for mortality.⁴ In the current study, we were particularly interested in cancers with a relatively good survival. There was no evidence to suggest rates of one of the commonest of these—malignant skin cancers other than melanoma—were higher in Porton Down veterans, even after we reclassified neoplasms previously coded as in situ or of uncertain or unknown behaviour. Porton Down veterans did, however, experience increased rates of ill defined, secondary or unspecified malignant neoplasms, in situ neoplasms, and neoplasms of uncertain or unknown behaviour. Such findings are difficult to interpret in the absence of information on smoking habits and other risk factors for cancer.

We identified almost 500 different chemicals in the records at Porton Down for 1941-89.³ We focused on nine specific chemicals to which the largest numbers of veterans were exposed. Given the large number of outcomes and exposure groups, some of the associations found might be due to chance. Of the nine chemicals, sulphur mustard and benzene are known human carcinogens, while nitrogen mustard is a probable carcinogen.⁶ Of these, the chemical most often used in tests was sulphur mustard, a carcinogen known to affect the upper and lower respiratory tract.

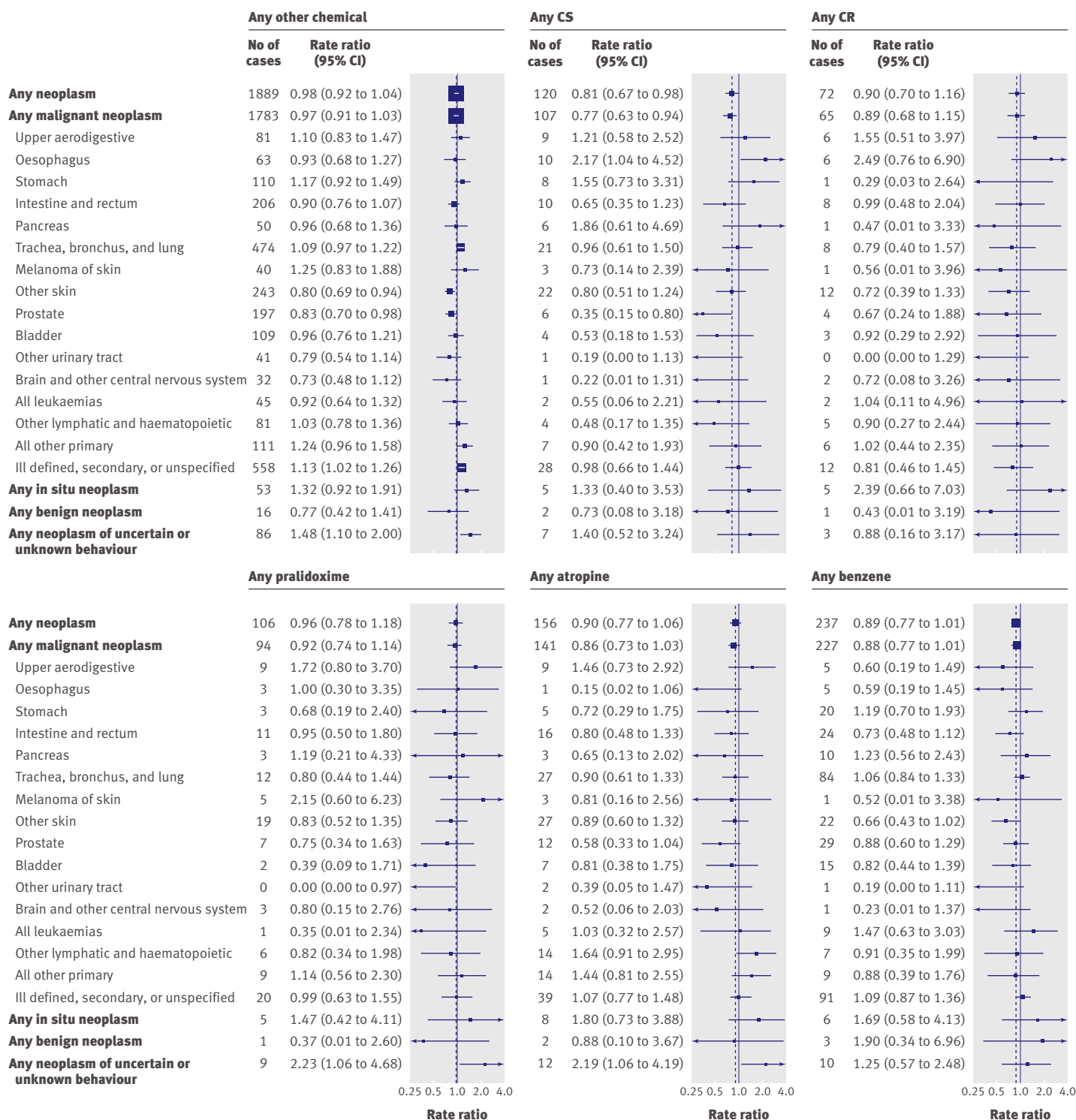


Fig 3 | Rate ratios for selected cancer sites or types in Porton Down veterans included in tests involving chemicals other than vesicants or nerve agents relative to all non-Porton Down veterans, adjusted for age group and calendar period. Rate ratio estimates are represented by box with size inversely proportional to variance. Vertical dotted line shows the estimate for any neoplasm

Over half of Porton Down veterans were included in tests involving this chemical but they experienced no increased cancer morbidity, either overall or for any specific cancer. This probably reflects the low cumulative exposures received, especially compared with those of manufacturing workers in whom excesses of

upper and lower respiratory cancer have been reported.^{9,10} In addition, use of physical protective barriers (such as masks and clothing), which were recorded as used in over 30% of tests involving vesicants,³ will have reduced the actual exposure of veterans to these chemicals.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Many tests in the Porton Down research programme into chemical warfare agents involved known carcinogens

WHAT THIS STUDY ADDS

Overall cancer morbidity was no higher in military personnel who had been included in tests at Porton Down than in those who had not been included or in the general population

Despite it being a known human carcinogen, there was no evidence of an overall excess of cancer in veterans exposed to benzene. Previous epidemiological evidence indicates an association between occupational exposure to benzene and leukaemia.⁶ Although the rate ratio for leukaemia was above unity, the confidence interval was wide and the rate ratio did not increase when we restricted analysis to veterans with two or more tests. The increased strength of association with skin cancer other than melanoma in veterans recorded to have high exposure to nitrogen mustard is noteworthy, given previous evidence that this chemical is a human carcinogen.⁶ This needs to be qualified, however, by the absence of an increase in those in whom the biological effect was high.

Although arsenic and arsenic compounds are human carcinogens,⁶ and Lewisite is an organic arsenic compound, there have been no previous epidemiological studies of the carcinogenicity of this specific chemical.¹¹ While there was no evidence of an overall excess of cancer in Porton Down veterans exposed to Lewisite, there was an excess of lung cancer, which was also present in our previous mortality analyses.⁴ The lack of association with increasing exposure or effect levels for this chemical, together with the lack of data on a known key confounding factor (smoking), make it difficult to attribute this excess to tests at Porton Down and it might be a chance finding.

For the other chemicals examined, there were no clear associations between any specific defined cancer type or site with sarin, pralidoxime, or atropine. For CS, while the overall cancer occurrence was lower than in non-Porton Down veterans, it was raised for cancer of the oesophagus, particularly in those who had two or more tests. A similar excess was seen in veterans exposed to CR, the other lachrymator included in our analyses.

In summary, the overall rates of cancer morbidity in Porton Down veterans were not raised relative to other veterans or the general population. The excesses of ill defined, secondary or unspecified malignant neoplasms, in situ neoplasms, and neoplasms of uncertain

or unknown behaviour were seen across several of the chemical exposure groups analysed and are difficult to interpret.

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- 1 Ministry of Defence. *Historical survey of the Porton Down service volunteer programme 1939-1989*. London: Ministry of Defence, 2006.
- 2 Evans R. *Gassed*. London: House of Stratus, 2000.
- 3 Keegan TJ, Walker SAS, Brooks C, Langdon T, Linsell L, Maconochie NES, et al. Exposures recorded for participants in the UK chemical warfare agents human research programme, 1941-1989. *Ann Occup Hyg* 2009;53:83-97.
- 4 Venables KM, Brooks C, Linsell L, Keegan TJ, Langdon T, Fletcher T, et al. Mortality in British military participants in human experimental research into chemical warfare agents at Porton Down: cohort study. *BMJ* 2009;b613.
- 5 Keegan TJ, Nieuwenhuijsen MJ, Fletcher T, Brooks C, Doyle P, Maconochie NES, et al. Reconstructing exposures from the UK Chemical Warfare Agent Human Research Programme. *Ann Occup Hyg* 2007;51:441-50.
- 6 International Agency for Research on Cancer. *IARC monographs on the evaluation of carcinogenic risks to humans*. Lyon: IARC. <http://monographs.iarc.fr/>.
- 7 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies. *J Natl Cancer Inst* 1959;22:719-48.
- 8 Clayton D, Hills M. *Statistical models in epidemiology*. Oxford: Oxford University Press, 1993.
- 9 Easton DF, Peto J, Doll R. Cancers of the respiratory tract in mustard gas workers. *Br J Ind Med* 1988;45:652-9.
- 10 Wada S, Miyaniishi M, Nishimoto Y, Kambe S, Miller RW. Mustard gas as a cause of respiratory neoplasia in man. *Lancet* 1968;i:1161-3.
- 11 Committee to survey the health effects of mustard gas and Lewisite. Pechura CM, Rall DP, eds. *Veterans at risk: the health effects of mustard gas and Lewisite*. Washington, DC: National Academy Press, 1993.

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