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Miscarriages and Congenital Conditions in Offspring of Veterans of the British Nuclear Atmospheric Test Programme

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Abstract

A postal questionnaire case-control study examined miscarriage in wives and congenital conditions in offspring of the 2007 membership of the British Nuclear Test Veterans Association, a group of ex-servicemen who were stationed at atmospheric nuclear weapon test sites between1952-67. Results were compared with a veteran-selected control group and also with national data. Based on 605 veteran children and 749 grandchildren compared with 311 control children and 408 control grandchildren there were significant excess levels of miscarriages, stillbirths, infant mortality and congenital illnesses in the veterans' children relative both to control children and expected numbers. 105 miscarriages in veteran's wives compared with 18 in controls OR=2.75 (1.56, 4.91; p=00016). There were 16 stillbirths; 3 in controls (OR=2.70 (0.73, 11.72; p=0.13). Perinatal mortality OR was 4.3 (1.22, 17.9; p=.01) on 25 deaths in veteran children. 57 veteran children had congenital conditions vs. 3 control children (OR=9.77 (2.92, 39.3); p=0.000003) these rates being also about 8 times those expected on the basis of UK EUROCAT data for 1980-2000. For grandchildren, similar levels of congenital illness were reported with 46 veteran grandchildren compared with 3 controls OR=8.35 (2.48, 33.8) p=0.000025. There was significantly more cancer in the veteran grandchildren than controls.

Whilst caution must be exercised due to structural problems inherent in this study we conclude that the veterans' offspring qualitatively exhibit a prevalence of congenital conditions significantly greater than that of controls and also that of the general population in England. The effect remains highly statistically significant even assuming a high selection bias in the responses and credibility is strengthened by the high rates of miscarriage reported by the veterans compared with controls, a result which could hardly have been due selection effects.

Keywords Ionizing radiation; Congenital malformation; Atomic tests; Cancer; Uranium

Introduction

The UK conducted Nuclear atmospheric weapons tests at Christmas Island (now Kiribati) and Malden Island in the Pacific and in Australia between 1952 and 1958; there were clean-up operations until 1967. The question of the health consequences of these exposures has been a matter of some debate and is currently part of legal cases before the Royal Courts of Justice [1,2] for which one of us (CB) was and is involved as an expert. The veterans themselves have been the subject of a series of epidemiological studies. In 1983, the Ministry of Defence (MoD) commissioned the UK National Radiological Protection Board (NRPB) in response to claims that the veterans were suffering radiation-related ill health. Some 21,000 personnel were located in MoD records as having taken part in the tests between 1952 and 1958 and these were matched with service controls by the MoD. Results showed a significant excess risk of leukaemia and also multiple myeloma [3]. A follow up [4] analysed cancer incidence to 1998 and showed a significant small excess risk from liver cancer incidence (RR 1.99 95% CI 1.19, 3.38) prostate cancer incidence (RR 1.22; 1.04, 1.43) and leukaemia mortality (1.83; 1.15, 2.54). Other studies of Australian [5] and New Zealand [6,7] test veterans showed higher levels of cancer and leukaemia risk than UK veterans, possibly because the UK controls suffered higher levels of fallout exposures than Southern Hemisphere controls [8].

The nuclear tests themselves were carried out at remote locations in Australia and in the Pacific. The megaton tests on Christmas Island in the Pacific involved thermonuclear devices air-dropped and detonated at altitude and others suspended by balloon [9]. All such tests produced fallout and rainout of radioactive material including Uranium, the main component. [10,11].

There are no contemporary measurements available of internal exposures to personnel stationed at or near the sites, nor of Uranium contamination. The extent and level of such contamination is a question of debate, especially since measurements were either not made at the time, or are still classified as secret by the UK government [1,2,11]. A Freedom of Information request for measurement data was made by one of us (CB) in 2009 but the documents were refused on the basis that the information might be of utility to a foreign power. Redacted secret data was supplied after a ruling made after application to the judge in case [2], the late HH Hugh Stubbs, and this indicated that the fallout contained very large fractions by mass of Uranium isotopes [11]. The sites and nearby areas have suffered residual contamination, thus there is potential for radiation related effects even in those who were there during, after and between detonations.

Some veterans who were believed to be at risk (near the detonation zone) at the time of the detonations wore film badge dosimeters. These devices registered prompt external doses from gamma radiation, but not alpha emitters like Plutonium and Uranium. Ionizing radiation is known to cause genetic and genomic damage in humans and causes increases in chromosome aberrations. Damage to germ cells can manifest itself as congenital effects in offspring. Such trans-generational effects have been shown to occur in animal studies [8,12] although curiously no such effects have been reported in the studies of the Japanese A-Bomb victims [8,13-16] a matter which we return to in the discussion section. An earlier study of the UK veterans [17] found excess congenital ill health in children, but unfortunately that study gave insufficient data to draw quantitative conclusions. At a meeting of the British Nuclear Test Veterans Association (BNTVA) in Blackpool, UK in 2006 attended by one of us (C B) many of the veterans expressed concern about possible effects in their children and grandchildren and the BNTVA commissioned the present study. The question of the trans-generational effects of internal exposures to the fallout from the nuclear tests is an important one as it raises significant political issues both about the effects of radioactive fallout on the veterans themselves, but also about the consequences on populations of the deployment of radioactive weapons.

Subjects and Methods

The population in the study was the 2007 registered membership of the BNTVA a support group of ex-servicemen and families which formed in 1983. The veterans of the tests were mainly national servicemen aged around 19 between 1952 and 1959 and the age range at 2007 of the veteran population was between 67 and 74. Many had died, and the remainder was elderly. In 1997 the membership of the BNTVA was about 2000 but the estimated membership whose addresses were still on the books of the BNTVA secretariat at the time of this study was about 1000 though it was not known by the secretariat whether these addresses were functional of if indeed the member was still alive. The secretary believed that a possible 50% of the addresses were either no longer correct or that the member was no longer alive but we have no independent evidence of this.

	Cases	Controls	Both
Number of valid returned questionnaires	280	132	412
Number of children reported	605	311	916
Number of grandchildren reported	749	408	1157
Number rejected due to duplication, incoherence, lack of critical information etc	28	12	40

Table 1: Number of veterans and controls and their children and grandchildren in the study group defined by the questionnaires

1000 questionnaires were posted to the last known address of members. The questionnaire asked details of the veterans' service number, branch, occupation in the services and present or immediate past occupation. It asked for details of participation in the A-Bomb Tests. They gave details of any miscarriages and birth outcomes, their children (birth dates and sex), the children's early health and later health and also the same details for the grandchildren. The method for obtaining controls was piloted earlier by us in a study of the Porton Down Veterans Support Group (unpublished). Each veteran was asked to recruit a control of approximately the same age to fill out a questionnaire which gave the same details. To avoid the element of choice of a control whose children were known to be healthy, or to avoid the reverse, of choosing controls whose children were not, we listed a sequence of choice of control as follows: (1) friend, (2) work colleague, (3) neighbour, (4) in-law, (5) other. This introduced an element of randomness to the choice of control. We permitted questionnaires to be filled in by spouses or children of veterans who had died. Table 1 gives the numbers of adults and children obtained through the questionnaires.

The health and various reported conditions of the offspring were then compared between cases and controls and also where possible with national average rates for the diseases and conditions being considered. The information obtained is listed in Table 2.

Information on veteran or control	Comment
1. Date of birth	
2. Main civilian occupation	
3. Army, Navy, Air force etc	
4. Duties?	
5. Which Test site?	Not for controls
6. Period at Test site?	Not for controls
7. Which tests witnessed?	Not for controls
8. Any physical reactions? Describe	Open ended; not for controls

9. Film Badge?	Not for controls
10. Diagnosed with Cancer or leukaemia	
11. If so which type and year diagnosed	
12. Smoked? Wife smoked?	
13. How many children?	
14. Children abnormalities?	
15. Any stillbirths, miscarriages, list	These entered separately and numbered
Information on each child	i.e. C(1,q) to C(n,q)
C1. Birth year and sex	
C2. Mother's birth year	
C3. Smoke prior to birth?	
C4. Birth problems? List	e.g. malformations, abnormalities, congenital defects, anything odd: open ended
C5. Child alive? Year of death?	
C6. Child cancer or leukaemia?	
C7. Type and when diagnosed	
C8. Any other major diseases in lifetime; describe	Open ended
Information on grandchildren	
G1. List grandchildren with ages and sex	
G2. Any birth problems/ hereditary conditions; list	Open ended
G2. Any cancer or leukaemia/ which type/ when diagnosed. Etc.	Open ended

Table 2: Offspring information questionnaires

We made two approaches to analysing these data. The first was to treat the exercise as a case-control study and compare conditions in the cases and the controls using conventional statistical methods to see if there were any statistically significant differences between the two groups. The total number of children or grandchildren reported as having congenital conditions was expressed as a rate and compared with the rate for the control offspring. We employed standard contingency tables for Odds Ratio and Chi-squared tests for significance, with Fisher Exact methods for small cells. This approach also enabled us to compare miscarriage rates for cases and controls, miscarriages being events for which there are no national data. The second method looked at expected values based on national data using the EUROCAT databases and compared these with the veterans' offspring.

In the case of cancer data we age-standardised the comparisons and compared cases with controls on the basis of 1997 national rates obtained from the Office for National Statistics (Series MB1).

Results

The questionnaires returned were generally well filled out and easy to interpret. There were some duplications and some were discarded for reasons of incoherence (Table 1). There was a significant amount of supporting information sent with many of the questionnaires, and much of the data obtained is not included here. We believe, from examining the responses and accompanying letters that the questionnaires were filled out honestly by veterans or their spouses who were concerned to discover whether their experiences at the test sites may have affected their children and grandchildren. We also believe, from examining the responses that the veterans were careful to ensure that they followed the instructions with regard to choosing controls, and that therefore there is no selection bias in the data obtained from controls. As the results will show, the control children and grandchildren do seem to have the same level of congenital illness rates as the national population, suggesting that their selection of controls was unbiased.

The main concern about the results with regard to drawing general conclusions is whether BNTVA membership is a biased selection from all the UK test veteran population still alive. A second concern is that those who responded to the mailout may be a biased fraction of the remaining number of veterans who received the questionnaire. For this reason, caution must be exercised in interpreting the results quantitatively. We return to this issue in the Discussion section.

Table 3 gives results for miscarriages, stillbirths and congenital diseases or other congenital conditions in the children and grandchildren of veterans and controls. Table 4 gives a list of all the conditions reported in the children which were included as likely to be congenital. Some of these (e.g. spina bifida) are clearly major accepted

congenital anomalies [18]. Others are less serious or more uncertain about the genetic origin. Conditions that could be caused by difficult births e.g. cerebral palsy were not included. Table 5 records whether the mother smoked before the child was born, whether the father was issued with a film badge to record external absorbed dose, symptoms noticed by the father at the test site, when the child was born and which test area the father was stationed at. Table 6 reports cancers in the offspring and controls. Miscarriage rates are presented in the analysis section, Table 7.

Reported	Veterans' (rate)a	Controls (rate)a	Odds ratio; 95% CI; p-valueb
Miscarriages	105	18	2.8 (1.56, 4.91) 0.00016
Number of children	605	311	
Stillbirths	16 (26.4)	3 (9.6)	2.7 (0.73, 11.72) 0.13
*Congenital defects	57 (94.2)	3(9.6)	9.8 (2.92, 39.3) 0.000003
Infant mortality	9 (14.9)	1 (3.21)	4.6 (0.6, 97.9) 0.18
Perinatal mortality	25 (40.3)	3 (9.6)	4.3 (1.22, 17.9) 0.01
All deaths all ages	41 (67.7)	10 (32.1)	2.1 (0.99, 4.51) 0.05
Cancer all agesc	16 (26.4)	5 (16)	Not significant
Cancer 0-14	2 (3.3)	0	Inifinite, Not significant

Table 3: Results for children; *see Table 5 for list of conditions included here; [a]rate per 1000 live births; [b]on Chi square test: Mantel Haenszel; Yates Corrected if cell contains less than 5 otherwise; [c] Excluding non-malignant skin cancer.

Conditions in Children of Veterans Total=57. Rate=94 per 1000 live births
1. Malformation of shoulders. Undescended testes
2. hip deformity
3. heart murmur and epilepsy
4. downs syndrome, heart murmur
5. congenital hip defect
6. heart murmur
7. congenital deafness in one ear
8. bi-corrulate uterus. No renal outline left side. Large kidney right side. Single ureter. These problems were highlighted at puberty. Surgery followed
9. Tumour on pituitary
10. born jaundiced. Epilepsy. Severe Disabled. Autistic
11. baby teeth malformed
12. cataracts to left eye at birth. Now blind in left eye
13. born with hydrocephalus
14. birth severe lymphangeomia and heomogena. Both breasts severely malformed. Right arm and hand disfigured. Serious birthmarks
15. with rough like sandpaper skin. Very small malformed feet. Poor immune system
16. Growth problems from age 5. skeletal and skull slow growth giving brain damage symptoms
17. wasted (not fully formed) muscle in right leg above knee
18. an extra side pocket found attached to bladder, which allowed urine to be retained and become infected. Found in 1970 by military doctors in Singapore.
19. problem with left eye at aprox 6 mos. Now blind in that eye
20. deformed spinal cord
21. malformation, curvature of the spine - also muscles missing on right side of chest
22. born with deformed left hand. 3 middle fingers missing.
23. one kidney.
24. double harelip. Double cleft pallet. No tendons in right leg. Toes on both feet malformed. Club foot. Fingers all malformed
25. very little sight in one eye - 4 yrs
26. very little sight in one eye - 1 yr
27. spina bifida
28. premature -born at 8 mos. Kyphoscoliosis 4 mos
29.curved spine
30. physical deformity of ear and hearing defect
31. stills disease. Diagn 1 yr
At 8yrs operation on both legs to allow heels to touch floor. No muscle fibre
32. heart murmur at birth
33. born badly deformed. Died shortly after birth
34. downs syndrome
35. severe lower leg deformity

36. right leg shorter, low b/w special care,
37. ovaries have not grown
38. Hole in stomach at birth; kidney probs at 6 yrs
39. deformed no genitals
40. balanced form of translocation in his chromosomes: 40 x y + (11: 21) @ 23. 1q 22.3 (diagnosed 2001 after birth of first grandchild)
41. vital organs not formed
42. heart murmur- birth to 3 months
43. Web neck. Profoundly deaf. Noises in the head. Very bad headaches since born.
44. spinal problem -hospital care for 2 yrs. Thyroid troubles on med
45. cyst of eyes at birth
46. Hole in eye (discovered later)
47. deformed feet.
48. heart murmur - diagnosed age 2
49. heart murmur 1 yr
50. mucopolysaccharide m.p.s3; sanphillipo disease
51. born w/ spina bifida, hydroencephalitis. Lived only a few hours
52. r/h hemiplegia at birth
53. hole in heart
54. born deaf
55. born with two additional thumbs and extra toes. Three joints in the two good thumbs
56. arms / shoulder joints not big to hold arm ball joints requiring operation
57. born with hole in heart
Conditions in Control Children (total=3) Rate=9.6 per 1000 live births
1. cleft palate
2. deafness in one ear. Poss congentital
3. congenital heart blockage

Table 4: Conditions noticed in first few years which are included for the purposes of this study as likely to be congenital and counted in Table 3 for both veterans and controls. Many reported possible congenital conditions were not included (These data are as reported in the questionnaires)

Number	Smoke	Badge	noticed after test	born	Test
1	0	0	back blistered	1967	5
2	0	0		1966	5
3	0	0		1959	5
4	0	0		1965	5
5	0	0	severe skin burns	1971	5
6	0	1	flu like symptoms	1970	5
7	0	0		1973	5
8	0	0		1966	5
9	0	0		1969	5
10	0	0	severe flu type illness, diarrhoea	1968	5
11	0	0		1964	5
12	1	0		1970	5
13	0	0		1959	5
14	0	0		1960	5
15	0	0		1963	5
16	0	0	sunburn, diarrhoea	1965	5
17	0	1	flu like/ lethargy/ hospitalised	1965	5
18	0	1	flu like illness	1967	5
19	1	0		1970	5

20	0	0		1966	5
21	1	1		1958	1
22	0	0	severe skin discolouration, diarrhoea	1963	5
23	0	0	severe skin discolouration, diarrhoea	1969	5
24	0	1		1963	5
25	1	0		1966	5
26	1	0		1968	5
27	1	0		1968	5
28	0	0	skin reddened	1967	5
29	0	1	diarrhoea, bleeding gums, bad headaches	1962	3
30	1	0		1968	5
31	1	0		1965	5
32	0	0	severe sunburn, diarrhoea	1961	5
33	1	0	diarrhoea,	1962	5
34	0	0	flu like illness, deaf, teeth bleeding	1978	5
35	0	0	skin boils, backache, peritonitis	1978	5
36	0	0		1978	5
37	0	0	skin rashes, diarrhoea	1960	5
38	0	0		1957	3
39	0	0		1967	3
40	0	1	severe sunburn,	1965	5
41	0	1	severe sunburn	1967	5
42	0	0	severe sunburn	1967	5
43	0	0		1966	5
44	0	0	open sores, hospitalised, coughing blood	1967	5
45	0	1	skin reddening	1957	1
46	0	1	skin reddening	1961	1
47	0	0		1972	5
48	0	1	hospitalised, flu like illness	1978	5
49	0	0	skin peeling, diarrhoea	1960	5
50	1	0	diarrhoea	1967	5
51	0	1		1962	5
52	0	0		1957	5
53	0	0		1967	5
54	0	0		1958	5
55	0	0		1962	5

56	0	0		1962	5
57	1	0	skin rashes, stomach upset, hospital	1970	5

Table 5: Further details of the children tabulated in Table 4. Next to the child ("Number" in first column) is whether the mother smoked before birth, whether the father was issued with a radiation badge, any symptoms father noticed after the tests or whilst at the site, when the child was born and which test series code. Code 5 is Christmas Island, others are Australia

Cancer site	Child born	Age diagnosed	Note
Veteran's Child; crude rate per 1000 is 26.4			
1. leukaemia	1969	20	
2. ovary	1958	48	Died 2006
3. breast	1966	35	Died 2003
4. melanoma	1963	44	
5. Hodgkin's	1967	23	
6. leukaemia	1968	33	
7. pituitary	1969	0	
8. ovary	1965	Not given	
9. Hodgkin's	1966	9	
10. cervix	1966	29	
11. lymphoma	1965	37	
12. glial/brain	1962	8	
13. carcinomatosis	1955	28	Died 1983
14. colon	1964	29	
15. cervix	1969	32	
16 melanoma	1976	31	
Control's child; crude rate per 1000 children is 16.0			
1. lung	1964	40	Died 2005
2. ovary	1963	21	
3.breast	1970	37	
4. Non Hodgkin Lymphoma	1967	Not given	
5. ovary	1962	43	

Table 6: Details of cancer in children of veterans and controls

Analysis

Miscarriages

Genetic or genomic damage in children cannot follow genetic stress to the parent in a continuous manner. This is a clear area where the dose-response relationship cannot be linear. This is because as the exposure increases there is a point where the damage to the foetus becomes too great for its continued development and it fails in the womb. The result is a miscarriage or stillbirth. The rate of congenital end point in the children then falls even though the exposure is increasing. This 'biphasic' curve has been described in radiation studies by Burlakova [18] and also by Busby [19-22] who reported the effect in a study of infant leukaemia after Chernobyl [23]. Radiation effects on the germ cells or embryo results in loss of either boys or girls and a perturbation in sex-ratio. Recent studies have indicated radiation induced sex-ratio effects after weapons fallout, near nuclear sites and after Chernobyl [24]. Sex ratio effects in the children of Japanese A-Bomb survivors were found to be dependent on the choice of controls [25]. However, in the case of the Japanese A-Bomb studies,

which began some 7 years after the bomb was used, no investigation of miscarriages was undertaken. Miscarriage is a traumatic and emotional experience for a mother and is seldom forgotten. For this reason it was of value to ask for the numbers of miscarriages which were remembered by the cases and by the controls. There were 105 miscarriages reported in 280 mothers married to veterans compared with 18 reported in 132 control mothers. Statistical results are given in Table 7 below.

	Miscarriages	**Number of mothers**
Veteran mothers	105	280
Control mothers	18	132
Odds Ratio=2.75 95% Confidence Interval 1.56<OR<4.91; p=0.00016 (Mantel Haenszel uncorrected)		

Table 7: Miscarriages: results and analysis

There was almost three times the number of miscarriages in the veteran mothers as in the control mothers. This is an interesting finding since it informs the question of selection bias: it is hard to imagine that the veterans would have selected themselves into the study on the basis of the number of miscarriages that their wives experienced. In addition, it suggests that were it not for these miscarriages, the heritable effects in the children may have been far greater.

Perinatal mortality and Stillbirths

Stillbirths reflect congenital effects in the foetus which result in death late in the pregnancy. Statistical comparison is made in Table 8. Although there was almost three times the number of stillbirths, this could have occurred by chance since the numbers were too small. Nevertheless, this result is in line with the miscarriage rates which make it most likely that there was a common cause for both. Combining stillbirths with early infant deaths provides significant perinatal mortality in the veterans' children, 25 cases with a rate of 40.3 per 1000 live and stillbirths compared with 3 cases in the controls with a rate of 9.6. The OR for perinatal mortality was 4.3 (1.22, 17.9; p=0.01).

	Stillbirths	**Number of births***
Veteran mothers	16	621
Control mothers	3	314
Odds Ratio=2.70 95% Confidence Interval 0.73<OR<11.72; p=0.103 (Mantel Haenszel uncorrected) Not statistically significant (numbers too small)		
	Perinatal mortality	**Number of births***
Veteran mothers	25	621
Control mothers	3	314
Odds Ratio=4.3 95% Confidence Interval 1.22<OR<17.9; p=0.01 (Mantel Haenszel uncorrected)		
*live plus dead births		

Table 8: Stillbirth and perinatal mortality: statistical results

Congenital conditions in the children and grandchildren

There were 57 cases of conditions which we classed as being congenital in 605 veteran children. This compared with 3 cases reported in 311 control children. Stillbirths are not included here although clearly these may have been due to a congenital cause. In making these classifications we generally excluded conditions which appeared later in life after ages 0-14 unless these were clearly congenital but detected late. The illnesses of the children taken over their whole lifetime to 2007 have not been compared in this preliminary report although we can carry out this analysis later. Statistical comparison of the children is given also in Table 3. There is almost ten times the incidence of disease that we class as congenital in the children of veterans compared with controls. Such an effect, if real and genetic (Mendelian), should be visible in the grandchildren also though to a significantly lesser extent. But as will be seen, the effect was almost as marked in the grandchildren. There were 1157 grandchildren in the study and results are reported in Table 9. The continuing high prevalence of congenital effects in the grandchildren was unexpected and we return to it in the general discussion.

	Conditions (rate/1000)	Number of children
Veteran children	57 (94.2)	605
Control children	3 (9.6)	311
Odds Ratio=9.77 95% Confidence Interval 2.92<OR<39.3; p=0.000003 (Mantel Haenszel uncorrected)		
Grandchildren Odds Ratio = 8.4 95% Confidence Interval 2.48<OR<33.8; p = 0.000025 (Mantel Haenszel uncorrected)		

Table 9: Congenital conditions in children of veterans and controls

Cancer in the children and grandchildren

Details of the analytical approach are given in results. Results, shown in Table 10, indicate that there was a slight excess risk of cancer in the children of veterans relative both to controls and to the national data but the effect was not statistically significant. The lifetime expected numbers of cancers was 12.8 in the children with 16 observed based on national incidence data, an Incidence Relative Risk of 1.25, not statistically significant (p=0.2). For the control children 6.1 cases were expected, with 5 observed. Veterans vs. Controls cancer Odds Ratio was 1.6 p=0.07. The interesting finding was that cancer in the veteran children was of significantly earlier age onset than in both controls and in national data. For children under 35 years at diagnosis there were 12 cases of cancer and leukaemia/lymphoma compared with 1 case in the control children, a crude rate ratio of 6.2 (p<0.01).

For the veteran grandchildren there were 4 cases of cancer reported with none in the controls. The OR is thus infinite but the numbers are small so caution should be exercised. On the basis of national rates we would expect 1.5 cases in ages 014 but 3 were observed RR=2.0 (Cumulative Poisson p= 0.2).

	Lifetime Expected	Observed	Relative Risk
Veteran children	12.8	16	1.25
Control children	6.1	5	0.8
There are no statistically significant increases in cancer relative to the national rates nor to the controls. The OR is 1.55 i.e. 55% more cancer in the veterans' children than in controls. p=0.07 (Cumulative Poisson). There is 25% more cancer in the veterans' children than the national rates would suggest p=0.2. There is 6.2 times the cancer rate in individuals under 35 yrs in the veterans' children than in the control children.			

Table 10: Cancer in the children of veterans and controls: All Malignancy except Non Melanoma Skin Cancer (RR based on national expected age specific rates).

Discussion

The studies of veterans' cancer carried out by NRPB [3,4] and those looking at Australian [4] and New Zealand [5] veterans did not examine the health of the children. The health of the offspring of the Japanese A-bomb cohorts have however been examined and appear to show no excess risk of cancer or other mortality [15,16] but there are problems with these conclusions which we discuss below.

There have been two previous studies of the UK atomic Test Veteran's health which also looked at their children, that of Rabbit Roff [17] in 1999 and Urquhart [26] in 1992. Both showed significant health effects. Since these support our results they are worth briefly reviewing.

The Rabbitt Roff Study

Rabbit Roff analysed an earlier questionnaire returned by 1041 members of the BNTVA in 1998 [17]. She was able to look at conditions in 2261 live born children and 2342 grandchildren. Regrettably there were no controls and the results were given in the final paper mainly as descriptions of the findings, without statistical comparisons with levels in a normal population. This reduces the utility of the study.

For example, 40 cancers are reported in the 2261 children but we cannot discover whether this is high or low or average since we do not have a breakdown of the children's birth years or the years of diagnosis. Unfortunately, the data and original paperwork on this important study have been secured by the University of Dundee who refuse to release them for any further analysis.

Table 11 contains some of the main results published in the literature paper. We have made some assessment in Table 11 of the expected numbers on the basis of the EUROCAT rates. It would be of interest to re-examine these data statistically to confirm whether these children and grandchildren have suffered what appear to be the same levels of genetic damage that we have found in our smaller group. But if we take the "conditions" to population ratio given then this is roughly the same for the children and the grandchildren which is what we also found for the congenital conditions listed.

The Urquhart studies

The first Urquhart study [26] analysed data from 158 families recording one birth defect per family and multiple births after fathers' exposure. The expected number in the first child was 61 and observed number was 80, (RR=1.3). The expected number in subsequent children was 97, observed 78 (RR=0.8). The comparison between these two groups gave an increased risk of 1.6. This was to test Gardner's hypothesis (advanced to explain the Seascale leukaemia cluster) that exposure of father within 6 months of birth caused heritable damage. The result, which was statistically significant ($\chi 2=9.6$; $p<0.001$), is valuable since it compares children born shortly after exposure to those born sometime after exposure.

The question of selection bias therefore does not arise as there is an internal control. However, the level of congenital illness difference between the two groups is modest and does not come close to the high levels of congenital illness we find in the present study, or that Rabbitt Roff found in the larger population she analysed in 1998.

Furthermore, if the effect was a genomic one and did not decay significantly between the births, this assumption may not be a safe one. Urquhart also carried out a study for the Sunday Mirror based on questions to the BNTVA. In this latter study, which was referred to in Hansard by Dr Ian Gibson on December 4th 2002, there was 3 times the expected number of birth defects found and seven Down's syndrome children, compared with one case expected after allowing for the age profile of the mothers.

	Children	**Our Comments**
Total	2261	
No health problems	1368	
"conditions"	893	Cannot comment without further description
Died as infants	53	No analysis; If true, rate is about twice expected
Cataracts	5	No analysis; If true rate is about 38 times normal (0.13 expected from EUROCAT, rate 0.59/10,000)
Excess and missing teeth	26	Also in this study
Early hair loss/ grey hair	11	Also in this study
Cardiovascular disorders	46	No analysis; 9.4 expected from EUROCAT for congenital heart disorders so RR=4.8
Cancers	40	No analysis.
Grandchildren		
Total	2342	
"conditions"	705	Cannot comment without further description
leukaemia	3	No analysis; need children's ages
Spina bifida	4	No analysis; 1.32 expected on EUROCAT rate
hydrocephalus	5	No analysis; 1.26 expected on EUROCAT rate
Downs syndrome	6	No analysis; need mothers' ages; 5 expected on EUROCAT
Hip deformity	11	No analysis; 0.2 expected

Table 11: Conditions reported in the Rabbitt Roff Study of BNTVA member's children and grandchildren [17]. Our comments: EUROCAT rates are for 5 combined UK registries 1980-2000.

The present study

The present study comes at a time when the veterans are aging and many have died. Besides looking at the children, there are enough data now to also examine the grandchildren. This is interesting for two reasons.

The first is that recent radiobiological research (carried out in the last 10 years and since the Rabbitt Roff and Urquhart studies) has identified a new phenomenon: genomic instability [27]. Genomic instability seems to be an evolutionary response to genetic damage. The organism reacts to a genotoxic stress (such as radiation) by inducing a random gene scrambling process.

Offspring (both at the organism level and the cell level) begin to show random genetic mutations. Studies carried out on animals and plants in the Chernobyl affected territories [28] show that these effects are heritable and continue for many generations. They do not fade away in the first generation (as a Mendelian process requires) but are some kind of inherited signal.

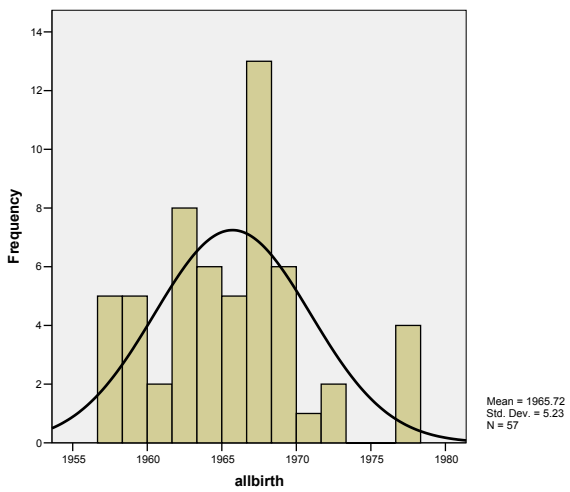

Figure 1: Distribution of the year of birth of the children of veterans with congenital disease

Next we look at stillbirth in the veteran children and controls (Table 3). Again the rate in the veterans is almost three times that of the controls but this result was not statistically significant owing to the small numbers. Nevertheless, the finding should not be dismissed for this reason as it follows from the logic applied to the miscarriage rates that it is a consequence of some genotoxic agent. Perinatal mortality rates were significantly higher in veteran children than in controls.

We looked at cancer in the children and found that there was slightly higher rate (1.25) than expected on the basis of a comparison with the national population. But the ages of diagnosis are earlier in the veteran children than the controls. The cancer effect seems greater in the grandchildren but numbers are too small for any firm conclusions. The children and grandchildren had not yet reached the ages where cancer rates increase sharply so little can be firmly said at this stage except that there does not seem to be any alarming excess of cancer in the children. Further research confirming this finding in the grandchildren would be valuable.

Selection bias

Based upon a mailout to 1000 addresses, the number of returned questionnaires was less than one third. However, the membership database employed was one that had not removed any members over the history of the BNTVA, an organization that began in the 1980s. Owing to the mean ages of the veterans in 2006 it can be assumed that a significant proportion of the membership had died or were no longer living at the same addresses which were on the database. The Secretary believed that as many as 50% of the addresses could be assumed to fall into such a category. For the remainder, perhaps 500 veterans it might be argued that there was a biased response, that those who filled out this questionnaire selected themselves on the basis of one or all of the following:

Their own ill health

A child's ill health

A grandchild's ill health

A stillbirth

Some of which circumstances may, we assume, lead them to want to ask whether the radiation exposures were a cause and select themselves into the study. We have already suggested that the high miscarriage rate provides an independent check on selection bias since it suggests the existence of a real genetic effect which cannot be a cause for selection into the BNTVA. The same is true for the high level of birth defects in the grandchildren, who were unlikely, have been born when the veteran joined the association. We assume that 1000 questionnaires were sent out but only 500 addresses were correct and the veteran was still alive. Then some 300 were returned by veterans, so even assuming that only veterans in the 500 with sick children responded we can multiply the anomaly rate by 3/5 and still find rates of congenital anomaly in the children and grandchildren significantly higher than the EUROCAT expected rate. Therefore we feel it is extremely unlikely that selection bias would operate in such a way to account for all these effects in the different areas. Further work on cross question analysis (Factor Analysis, Principal Component analysis etc) may help reveal relationship between the various components.

The causes of the effects

The nuclear test veterans had nothing in common apart from their location at the test sites. These were in Australia or on small Pacific Islands north of the equator. Genetic damage is not believed to be laterally transmissible. There were no known background environmental genotoxins shared by the different sites prior to the tests. Therefore the increased level of trans-generational genetic or genomic damage shown by these results (and those of Rabbitt Roff and Urquhart) is due a genotoxic exposure to fathers which was common to the test sites. This can only be ionizing radiation or some other component of the material produced by the explosion of atomic weapons.

Many of the veterans whose children and/or grandchildren were affected were at the sites between detonations and could not have been exposed to gamma radiation from explosions. Even those who were present and who wore film badge dosimeters showed gamma doses which were close to natural background. So as a cause we are left with residual radioactivity from fallout and/or some other genotoxic component of the bombs.

If residual radioactivity causes effects in the offspring of those internally contaminated though inhalation and ingestion then we might expect to find evidence in the offspring of those living in Hiroshima after the Atomic bombing in 1945. Therefore it is necessary to firstly address the studies of radiation, cancer and congenital illness in offspring carried out after the United States Atomic Bombing of Hiroshima and Nagasaki, the Radiation Effects Research Foundation (RERF) life-span studies. The methodology of the studies is interesting epidemiologically since from the beginning the built-in assumption was that any downstream effect could be characterized by comparing three groups of individuals characterized by different prompt external doses [29]. Thus there was an initial control selection choice which may have been unfortunate. At no stage did the RERF (or their predecessors the Atomic Bomb Casualty Commission, ABCC) compare their findings (birth effects, cancer) with the national population to obtain National Standardised Ratios. The doses were calculated on the basis of external prompt gamma ray exposures only,

it being assumed that there was no fallout or residual radiation. The three dose categories were high and medium (calculated on how far the individual was from the zero position of the detonation) and no dose, based on a group that was termed "not in city" NIC. This latter group was assembled from combining early and late entrants to the city after the bombing. The "high" and "medium" doses were extremely high, and the upper end of the "high" doses caused death in a number of individuals so exposed.

An analysis of the birth defects in the three groups shows no significant difference between them, leading the RERF to conclude that there was no effect of the radiation on adverse birth outcomes. This has led to the current belief [30] that there is no excess risk of adverse genetic effects in offspring below the dose level of 100mSv. But RERF's belief that there was no residual fallout and rainout components of the bomb is incorrect since Uranium and other fallout components were indeed measured in the cities [31,32] and recent studies of non-cancer effects (skin burns, diarrhoea, epilation) after the bombing in those who were several kilometres from the zero point indicates that there were radiation effects in those who lived too far away for these to be due to prompt gamma exposures [33,34].

Additional evidence for a control group error comes from studies of the sex ratio. Genetic damage from ionizing radiation is characterized by a change in the sex ratio, the number of boys born to 1000 girls, normally about 1050. Sex ratio studies of the children of the A-Bomb victims were undertaken along the same lines, using the same groups. The effects were found to be equivocal and the study was abandoned. However Padmanabhan has re-examined the sex ratios in the A-Bomb series and shown that there are differences which depend on whether the NIC Early Entrants or the NIC late entrants are employed as the zero dose control group [25].

Since radiation film badges worn by those most likely to have been exposed have not generally shown absorbed doses very different from background, the MoD have consistently argued that no increases in cancer could possibly have occurred as a result of any exposures at the test sites and this is the general nature of the defence in the court cases [1,2]. However, the risk model relied on by the MoD is that of the ICRP which is based on the cancer yield of the survivors of the atomic bombing of Hiroshima and Nagasaki [30].

There have been many criticisms of these studies and their applicability to the internal exposures which were received by the test veterans [37-41]. The main criticism is that these studies are silent on exposure to internal radioactivity from fallout including Uranium, since both exposed and controls were equally affected [20-22,31-34,40,41]. If such materials convey much greater levels of hazard per unit dose then these studies are unsafe for such exposures [22,40]. A contribution to this discussion is a recent study [19,42] which reported a significant excess level of chromosome aberration in New Zealand test veterans. Although it is conceded that there is no secure published direct link between measured levels of chromosome damage and clinical effects in the organism or in populations, yet it must be also conceded that chromosome damage is a consequence of exposure to genotoxins and especially to prior radiation exposure, an event which is associated in the literature with clinical expression of genetic-based conditions like cancer and congenital effects. Thus it is biologically plausible at minimum that there could be expected to be increased levels of foetal loss, stillbirths and congenital anomaly expressed in offspring of test veterans who had excess chromosome damage. Or to reverse the argument, it is not surprising that the test veterans, who show these high levels of trans-generational genetic damage as a group, also seem to have excess chromosome aberrations.

If the congenital conditions were caused by external radiation in the sample we have examined, then we might have expected the rate to be high in the early 1960s and to fall off later on. It would be an acute external irradiation effect on the sperm producing apparatus. We should expect the distribution of birth year of the congenital anomaly children to peak earlier than that of the whole sample.

But it does not appear to do so. We would also expect a correlation with film badge dose. There is none. This suggests that the real effects are a either result of a contamination process with some genotoxin with some long biological halflife (e.g. Uranium particulates which have a halflife of up to 20 years [43]) or on the other hand, a process like genomic instability induced in germ cells representing an epigenetic switch. The effects in the grandchildren support this latter explanation.

Studies of radiation exposure have historically concentrated upon external acute exposure. The NRPB style studies of the veterans used film badge dosimeter doses [35]. The Japanese A-Bomb studies employed calculation of external dose and distance from hypocentre of the explosion. The last ten years have seen an increasing focus on the effects of internal exposure to radioactive elements and particles, inhaled and transferred across the lung to the lymphatic system.

This has been found necessary to explain the many anomalous findings of cancer and congenital illness in those exposed to these pollutants near nuclear sites, nuclear test sites and accidents like Chernobyl at very low "doses", as conventionally calculated. The matter of the adequacy of "dose" for radiation protection from internal radionuclides is discussed at some length in ECRR2010 [40], CERRIE 2004 [21] and CERRIE Minority Report 2004 [20], IRSN 2006 [41], ECRR2006 [26] and Busby 2013 [22]. It was pointed out explicitly in the CERRIE documents that for internal exposures for certain nuclides the concept of absorbed dose is meaningless and ICRP 103 [30] also concedes this. The question of "absorbed dose" and radionuclide exposures and their current protection models is discussed in Busby 2012 [22] and in ECRR 2010 [40] and we will not further address the issue here.

Conclusions

In conclusion, we argue that the results of this study support the belief that involvement in the Nuclear Tests caused increased rates of genetic-based illness in both the children and grandchildren of veterans. This may be by induction of trans-generational instability. We suggest the cause is internal exposure to radioactive contamination at the test sites, particularly to Uranium. Further research in this area would be welcome and might include (1) further studies of health in the offspring of the veterans and (2) chromosome aberration analysis of the veterans themselves and also (3) measurements in tissue samples (bone, teeth) of Uranium isotope ratios. We would also urge mthe University of Dundee to release the 1998 BNTVA Rabbitt Roff survey data for further analysis. £1000 was contributed towards the cost of the study by the British Nuclear Test Veterans' Association whose members organised the distribution of the questionnaires. Neither of us have any conflict of interest. We are grateful to Tony Boys for assistance with obtaining and interpreting Japanese vital statistics.

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