Mortality and health effects in participants of atmospheric nuclear weapons tests: A critical review.

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A report presented to The New Zealand War Pensions Medical Research Trust Board

1997

This report presents the results of a critical review of literature relating to the service of New Zealand Navy personnel at Christmas and Malden Islands in Operation Grapple 1957-1958. The purpose of the report is to provide the War Pensions Advisory Board with information which may be used in the evaluation of guidelines for assessment panels and to inform decisions concerning further research which may be undertaken with New Zealand atomic veterans.

The intention was not to provide a "state of the art" review or comprehensive critique of all aspects of atomic radiation research. The relatively narrow focus is on published research papers with close reference to the Christmas Island and Malden Island nuclear explosions, and includes other literature related to like situations. The material was sourced primarily from reports by acknowledged authorities in the field and articles published in peer-review journals. The review did not include primary source material, such as Department of Defence archival documents. Unless otherwise considered as essential material, the review focused on the most recent research papers presented since 1990.

The report consists of 4 sections, the first of which provides an executive summary. The second presents a discussion of a number of methodological issues which should be considered in relation to research on the effects of low-level ionizing radiation with particular reference to research involving the atomic veteran cohort.

A general overview of this research is provided in section 3. Presented in roughly chronological order, research is reviewed from the initial study of "Smoky" veterans

undertaken by the Centers for Disease Control in the 1970s to the most recent Medical Follow-up Agency research on Operation CROSSROADS participants published in 1996.

Overall there are few studies which are specifically concerned with long-term health effects of participation in nuclear weapons testing programmes. Because most of the research has been concerned with the examination of mortality rates and causes, there is little data available relating to the incidence of disease in these veterans. Consequently, the report also provides a summary of data from recent incident studies of atomic bomb survivors.

The final section provides detailed summaries of four studies which were considered to be the most significant in terms of impact or recency of publication. In addition to the major findings, the summaries include notable sampling, methodological and interpretive issues. Details of recent A-bomb survivor research are also presented.

Acknowledgement

This review was supported by a grant from The New Zealand War Pensions Medical Research Trust Fund. The author wishes to acknowledge the assistance received from Margaret Faulkner of the New Zealand Income Support Service and Peter Robinson from the War Pensions Advisory Board. Thanks are also due to Trevor Humphrey and Janet Dixon of RIMPAC and Roy Sefton of NZNTVA for their helpful contributions.

Contents

■ **Methodological issues:**

Atomic veteran studies vary in the extent to which they address methodological concerns. Interpretations of reported data must be made with caution bearing in mind:

- Definition of study cohort and validation of control group; adequate control for confounding variables and sampling biases.
- Appropriateness of proportionate mortality methodology, especially the calculation of relative risks from standardized mortality ratios
- Unreliability of dosimetry based on film badge data - a satisfactory dose reconstruction methodology is still to emerge.
- Accuracy of death certificate diagnoses may be low and varies according to age, and cause and place of death.
- Dangers of extrapolation of risks from one population to another

■ **Major research findings:**

- ***Proportionate mortality data:***
- Suggest that the all-cause mortality for atomic veterans does not differ significantly from national rates.
- Findings for all-cancer mortality and site-specific cancer mortality are inconsistent.

- ***Comparative mortality data:***
- Suggest that all-cause and all-cancers mortality varies little between participants and controls, however, two studies reported an excess in overall participant mortality.

- There is some indication of excess mortality in participants from:
  - diseases of the digestive system, particularly cirrhosis of the liver (Raman, 1987).
  - cancer of the digestive organs (Watanabe, et al. 1995).
  - leukaemia, multiple myeloma and cancer of the bladder (Darby et al., 1988).
  - haematological cancer, in particular leukaemia (Pearce, et al., 1990; 1996).

- The most recent, and arguably the most rigorous study, found no significant differences for any of the 44 causes-of-death examined (MFUA, 1996).

- ***Incidence data:***
- Only 3 veteran studies reported incidence findings:
  - Overall cancer incidence in participants was lower than national rates, the incidence of leukaemia was higher (Caldwell et al., 1983)
  - Compared to controls, there was no significant difference in incidence of all neoplasms, but higher rates of liver cancer, cancer of the bladder, and leukaemia, and lower rates of non-melanoma skin cancer in participants (Darby et al., 1993b).
  - Pearce et al. (1990; 1996) reported an increased incidence for all-haematological cancers and leukaemia in particular among participants compared to controls.

- Recent A-bomb survivor incidence data shows an excess risk among survivors for:
  - Solid cancers combined, specifically for cancers of the stomach, colon, lung, breast, ovary, urinary bladder, thyroid, liver, salivary gland and non-melanoma skin cancer.
  - acute lymphocytic leukaemia, acute myelogenous leukaemia, and chronic myelocytic leukaemia, and;
  - uterine myoma, chronic liver disease and cirrhosis, and thyroid disease.

■ **Summary of previous findings:**

There are some indications that test participants may have an increased risk of:

- developing haematological cancers (especially leukaemia); liver cancer; and cancer of the bladder.
- death from haematological cancer (especially leukaemia); multiple myeloma; cancer of the bladder; and cancer/disease of the digestive system.

- These findings are not consistent across studies, and it has been suggested that excesses may be due to chance or to factors other than radiation.

- Most researchers concluded that there was little or no evidence for a clear association between radiation exposure and increased mortality or cancer risk among atomic veterans:

  - the results did not support claims of a higher frequency of death from all causes or from cancer among exposed Canadian military personnel as a group (Raman et al., 1987).

- participation in the U.K. nuclear weapons testing programme had no detectable effect on risk of developing cancer or other fatal diseases (Darby et al., 1993a).

- participation in Operation Grapple did not result in a detectable increase in mortality from causes other than cancer and there was little evidence of an increased risk for non-haematological cancers (Pearce et al., 1990b; 1996a).

- there was no evidence for elevated rates of suspected radiogenic cancers among Hardtack participants (Watanabe et al., 1995).

- the findings did not support the hypothesis that exposure to ionizing radiation caused increased mortality among CROSSROADS participants (MFUA, 1996).

Comments and Recommendations

Taken together, the findings of published research provide no clear evidence or consistent pattern of increased mortality and cancer risk among atomic veterans, despite a number of suggestive findings.

The most consistent evidence was that pertaining to an increased risk in test participants for haematological cancers, in particular leukaemia. There were also indications that test participants may have an increased risk of multiple myeloma and cancers of the bladder, digestive system and liver. However, the results were inconsistent, and given the low recorded doses, the small size of expected excesses, and dosimetry problems, it is difficult to interpret such excesses as being due to radiation exposures.

Clearly further research is required which attempts to unravel the intricacies of the association between radiation exposure and health effects in participants of atmospheric nuclear weapons tests. Two further studies which are currently in progress should provide a major step forward in this quest (see MFUA, 1996; Roff: personal communication).

The merits of further epidemiological research on the New Zealand cohort needs to be questioned. The feasibility of such research is dependent on the degree to which certain methodological difficulties can be addressed.

The New Zealand cohort is very small and the impact of sample size on the subsequent power of analysis can not be overlooked. A well defined participant/control cohort is essential. There has been some debate, however, about the validity and completeness of previous ascertainments of participation and possible "exposure". In the absence of reliable dose

estimate data, and the inability to use surrogate exposure groups, findings could not be related to exposure levels. Finally, any examination of mortality rates and causes must address the reliance on data derived from death certificate information and investigate alternative sources from which the data could be validated.

Conclusions derived from group data cannot be extrapolated to individual cases, the findings of this review in no way discount the problems experienced by individual veterans or their families. Indeed, the psychological impact of exposure and perceived risk might provide a fruitful avenue for future research exploration.

Recommendations:

- At present research evidence relating specifically to atomic test veterans is insufficient to support significant changes to the current assessment guidelines.

- Because of the serious methodological issues which must be addressed, further epidemiological research on New Zealand atomic veterans is not feasible at this time.

In their report on the health effects of exposure to low-dose radiation, the National Research Council's Committee on the Biological Effects of Ionizing Radiation noted that a number of low dose studies have reported risks that are substantially in excess of those estimated by the committee, including risks of populations exposed to fallout from nuclear weapons tests (BEIR V, 1990). The discrepancies between the low-dose study estimates and those based on high dose studies could arise, the report maintains, from problems of extrapolation, or an inappropriate design, analysis, or interpretation of results. In other words, from methodological limitations. There are a range of methodological issues which are important to consider before reviewing or undertaking research on the effects of low-level ionizing radiation. This section will briefly consider a number of these issues in relation to research involving the veterans of atmospheric nuclear weapons tests and experimental programmes.

Sampling variability

The problem of random error caused by sampling variability is particularly important in low-dose studies which frequently utilise correlational or case-control methodologies. While ecological correlational studies are probably the most susceptible to confounding, case-control studies generally offer the greatest opportunity to control for confounding by matching or obtaining information on definable covariates for use in analysis (BIER V, 1990). However, the extent to which this has been done varies across studies.

The results of case-control studies hinge on differences between the two (or more) groups being compared. The appropriateness of the comparison group is, therefore, of central concern. Information bias leading to misclassification of either exposure or disease status, if random, leads to underestimated risk (MFUA, 1996).

Regardless of the outcomes under study, it is imperative that attempts are made to identify and locate all subjects in both the participant and control/comparison groups. There are a number of generally acceptable rules or protocols which researchers follow in order to minimise the risk of sample bias. MFUA (1996) offer a useful summary of these which includes:

* ensuring an equal likelihood of finding records of people in each group; if data is available for only one group, do not use it.
* being aware of biases built into record systems. There are potentially many: people with illnesses are more likely to seek care; data accuracy is associated with the level of ascertainment, such as completeness of fact-of-death, date-of-death, or cause-of-death information.
* using a firm cut-off date for the follow-up period. It is necessary to treat participants and comparisons equally in terms of data collection, follow-up, and maintenance.
* recognizing that raw numbers offer different information than do rates or proportions. The latter include a context for interpreting the importance of the raw number. While reporting the number of people dead is often informative, it is insufficient to use *percentages* without first identifying a conceptually acceptable denominator and then using the *entire* denominator in any calculation (MFUA, 1996, pp. 15-16).

Healthy Soldier Effect

The "healthy soldier/worker effect" refers to the expectation that, because of physical and medical fitness selection criteria, a cohort of workers or soldiers will be healthier than a general cohort, as reflected in morbidity and mortality rates. The effect has been well documented in disease-exposure studies which have also shown that while the healthy soldier effect is most pronounced in measurements taken close to the time of entry into military service, it continues for decades (MFUA, 1997).

The use of a military comparison group can address the healthy soldier effect but does involve drawbacks. As the MFUA (1977) point out, while Government and other groups routinely gather statistics on general populations, data are not readily available for more precisely defined comparison groups in the military or elsewhere. The use of a specifically designed comparison group is, therefore, an expensive and time-consuming exercise which also increases the opportunity to introduce confounding information that could bias the findings (MFUA, 1996).

The debate surrounding the healthy soldier effect is well illustrated with reference to the MFUA Five Series Study (Robinette et al., 1985). Bross and Bross (1987) maintain that although the problem was discussed in the original report and a method of correcting it was described, false negative results were reported because no correction was actually made. They suggest that one way to compensate for the healthy soldier effect would be to do what is termed a "dosage response analysis". Most simply this would entail a comparison of the survivorship at the higher reported radiation doses with that at the lower radiation doses (Bross & Bross, 1987). Such a comparison, they maintain, would also eliminate the "dosage bias". That is, because many of the test participants in the MFUA study had reported radiation doses below the levels at which health effects would be detectable, the failure to take dosage into account would dilute the radiation effects.

Even with the use of dosage response analysis, radiogenic effects could be masked by two further biases which dilute observed radiation effects in the data (Bross & Bross, 1987). First, the "latency bias" results form the inclusion of deaths that occurred during the latent period (e.g. for solid cancers within about 15 years from exposure). Second, the "mixture bias" refers to the use of cause of death categories that mix radiogenic and non-radiogenic causes of death. It is generally accepted, for example, that non-lymphatic leukaemias are often

radiogenic but lymphatic leukaemias are not. According to Bross and Bross (1987), the failure to separate the two kinds of leukaemia in the MFUA report, in effect, halved the reported risks for the radiogenic leukaemias.

Proportionate mortality studies

The appropriateness of proportionate mortality studies for assessing relative risk outcomes in in nuclear test participants has been questioned. Roff (1997) contends that such studies are unsuitable for establishing the real relative risks of veterans' exposures to the hazards of ionizing radiation in weapons tests and that a more refined methodology for the study of clusters in specific cohorts is needed. Others advise a careful interpretation of the results of proportionate mortality studies since a proportionate excess may reflect either an excess in the absolute rate for a disease, or a deficit in the absolute rates for other causes (IOM, 1994).

In the Pearce et al (1990a) study, for example, standardized mortality ratios (SMRs) were calculated by taking the observed mortality for each outcome then dividing that by the expected mortality. The relative risk (RR) for each outcome was then estimated by taking the SMR in the test participants and dividing it by the SMR in the controls. It has been argued that such calculations are bound to underestimate the relative risk which are a dependent function of the SMRs (Roff, 1997). Bross and Bross (1987) point out that it is not the ratio itself which is at fault, but rather it is the data base to which it is applied that causes the problems. When the comparison involves subgroups that are selected for health-related reasons, SMRs do not, they argue, provide scientifically and statistically valid comparisons (Bross & Bross, 1987).

Roff also argues that the convention of calculating the relative risks of two cohorts of veterans as a dependent function of the SMRs for each cohort in proportionate mortality studies does

not allow sufficiently for either the healthy soldier effect or for particular features of a given cohort's profile. Furthermore, she maintains that mortality rates and the latency of morbidity for a particular cohort are not adequately signified by the comparison with the generalised information from the general population (Roff, 1997).

Despite the difficulties associated with proportionate mortality methodologies they are commonly used and do have some positive aspects. The comparison of the rates of a cohort of interest with those of a stable, known, and usually larger population mean that the larger population rates help to stabilise estimates of rare disease or within sparse subject strata (MFUA, 1996). Furthermore, SMRs allow for informal comparisons between studies and assist in placing the relative rates in a familiar perspective for readers (MFUA, 1996).

Accuracy of death certificates diagnoses

The overall accuracy of death certificate diagnoses has been questioned in numerous studies. In a recent example, Ron et al., (1994b) used data from the Atomic Bomb Casualty Commission/Radiation Effects Research Foundation (ABCC/RERF), series of over 5,000 autopsies to examine death certificate accuracy for 12 disease categories and to assess the effect of potential modifying factors on agreement and accuracy. The results showed that the death certificate accuracy was low and that it varied widely depending on cause of death, age, and place of death (Ron et al., 1994b). The overall percentage of agreement between death certificates and autopsy diagnoses was only 52.5%. The highest detection rate was for neoplasms, yet almost 25% of cancers diagnosed at autopsy were missed on death certificates. Confirmation and detection rates were above 70% for neoplasms and external causes of death only. Overall agreement decreased with increasing age at death and was worse for deaths occurring outside the hospital (Ron et al., 1994b).

Death certificates will continue to be an important source of data despite the obvious difficulties and errors associated with their use because they offer certain advantages. They are usually required by law and, compared to other records, are relatively complete. Furthermore, incidence data are difficult to collect and more accurate mortality data are seldom available.

Multiple comparisons

The problem of multiple comparisons arises when a large number of statistical tests are used. Such a process increases the likelihood of findings being labelled statistically significant due to chance and invalidates the conventional value quoted for the test of significance (BIER V, 1990; MFUA, 1996). Efforts made to limit the number of statistical tests usually involve specifying, in advance, relatively small numbers of tests which focus on a limited number of research questions. However, as MFUA (1996) point out, there are times when numerous independent tests are made and it is important to remember in such cases that statistically significant results may be so labelled merely due to chance. It is also important to consider that a true association may fail to test as statistically significant because of lack of statistical power. The power of a study to detect existing real differences is dependent on sample size, the incidence of the outcome in the absence of exposure, and the strength of the association between the exposure and the outcome (MFUA, 1996). The interpretation of multiple comparison results must, therefore, be guided by prior hypotheses and by the consistency of results with other studies (BIER V, 1990).

Dose reconstruction

The clarification of actual exposure levels among test participants is a highly problematic aspect of research with this veteran cohort. Official British and U.S. reports suggest that recorded levels of ionizing radiation during and following nuclear weapons tests were very

low, however, serious misgivings have been voiced regarding the measurement and recording of radiation exposure data during nuclear weapons testing (ACHRE, 1995; Bullman & Kang, 1994; Roff, 1997). It appears that much of the data on which the dose estimates are based is highly questionable.

The 1995 report of the Advisory Committee on Human Radiation Experiments (ACHRE) presents U.S. Department of Defence (DOD) data which shows that less than 14% of the 17,062 Upshot Knothole (1953) series participants are known to have been issued with film badges as personal dosimeters. Similarly at Desert Rock V, on the basis of the Army surgeon general's policy that one-time exposure need not be reported, it was determined that manoeuvre troop units would be issued one film badge per platoon, and observers would be issued one per bus (ACHRE, 1995). The Committee also reported that a recently declassified DOD memo relating to Desert Rock V records that although film badges on the officer volunteers indicated an average gamma dose of 14 roentgens, the best information available suggests that the true dose was probably 24 rem initial gamma plus neutron radiation (ACHRE, 1995).

Because of the numerous vagaries and inconsistencies surrounding the use, storage and recording of film badges, dosimetry based on them is unreliable. The Medical Follow-up Agency, for example, considered that radiation dose estimates currently available (largely based on film badge information) were unsuitable for epidemiological analysis, and the study utilised exposure surrogate groups instead (MFUA, 1996) .

Roff (1996) goes further and argues that previous determinations were frequently made on "anachronistic understandings of the relation between distance and hazards from fallout", and that, there is still no reliable method for reconstructing doses (Roff, 1997). She criticises the

manner in which our understanding of fallout has evolved over the past 50 years and documents, in *Hotspots*, the way in which an "article of faith" developed among the Atomic Bomb Casualty Commission (ABCC) researchers to the effect that there was no residual radiation in either Hiroshima or Nagasaki (Roff, 1995). She documents how this "article of faith" skewed subsequent studies as the researchers entered into a series of self-confirming "critical closures" in both the collection and interpretation of data on the long-term effects of the bombs (Roff, 1995).

She contends that a similar understanding of fallout is apparent in the studies of nuclear testing in the Marshall Islands and the Pacific, illustrating a "naïve belief that only those who directly touched known radioactive equipment such as the aircraft which flew through the detonation clouds could have absorbed, inhaled, or ingested radionuclides" (Roff, 1997, p. 56). By way of example, she quotes Darby et al (1993) who comment that the excess mortality found in a similar study of New Zealand personnel (Pearce et al., 1990) is "difficult to attribute to the tests. According to the Ministry of Defence, the ships of the RNZN were at least 40 km from the detonations and so would not have been irradiated directly".

At the request and under the direction of the National Cancer Institute, Oak Ridge Associated Universities undertook a review of the devices and techniques that may be useful in determining previous radiation exposure. Four working groups were formed to review the applicability of biological indicators and of bioassay, whole-body counting, and cytogenetic techniques in radiation dose assessment (Bender et al., 1988). There are two categories of the "applicable devices and techniques": those which measure residual effect of radiation exposure on the biological system; and those which measure residual quantities of the radiation source in the body. However, it seems that many of these either are applicable only to the detection

of relatively high radiation exposures or must be employed at relatively short periods following exposure (Bender et al., 1988).

The measurement of cytogenetic changes in cultured lymphocytes is a well-established methodology for estimating the magnitude of a dose of ionizing radiation to which an individual has been exposed. After reviewing the accumulated data, the cytogenetic working group concluded that the technique has utility when employed at relatively short periods after exposure, but that it is incapable of providing meaningful estimates of radiation doses to individuals exposed 25-42 years ago (the time of elapse for nuclear test veterans at time the report was prepared) (Bender et al., 1988).

In addition to the cytogenetic technique, other potential biological indicators of radiation dose have been sought in studies of blood, urine, cells, cell cultures, tissues, and organs. The biological indicators working group concluded that such assessments may indicate damage caused by radiation at early times after exposure, but that, even with further developments, it is doubtful that they will be useful in determining radiation dose years or decades after exposure (Lushbaugh, et al., 1991).

With respect to "whole body counting" Toohey et al. (1991) used the term to refer to the measurement of radionuclides in the entire body, but not specific organ counts. Whole body counting determines the amount of radioactivity present in the body at the time of measurement, it cannot directly determine the amount present at some previous time; that quantity must be inferred from the measured body content and from the application of metabolic models or retention curves that describe the behaviour of radionuclides in the body (Toohey et al., 1991). Consequently, measurements made many years following exposure can be very difficult to interpret. The working group acknowledged that the development of new

detectors offers some hope, but they were doubtful that such improvements would be sufficient to meet the need of assessing radiation exposures that occurred decades earlier (Toohey et al., 1991).

Perhaps the most promising avenue for reconstructive dosimetry lies in bioassay techniques which provide an indirect assessment of how much of a particular radionuclide is present in the body at time of sampling. Mathematical models are then used to estimate currently retained body burden, the initial body burden when uptake occurred, and the cumulative dose estimates received by various body organs and tissues (Boecker et al., 1991). The bioassay working group concluded that models of these types, available for use for ^{90}Sr and ^{239}Pu, appeared to be reasonable for the interpretation of bioassay results for intakes that may have occurred 25-40 years ago. They note, however, that current techniques will detect these radionuclides only if the amount excreted is approximately twice the background levels due to worldwide fallout (Boecker et al., 1991).

Extrapolation

Assessments of the risks of low-level irradiation are highly uncertain and have been the subject of ongoing debate and controversy (Upton, Shore, & Harley, 1992). Especially contentious is the belief that effects at low doses cannot be directly studied, and that a slow dose rate reduces the carcinogenic effect of ionizing radiation exposure (Bertell, 195). As a consequence of such assumption, there has been a reliance on high-dose studies, and the A-bomb survivor studies have come to be regarded, inappropriately some would argue, as "benchmark" studies (e.g. Roff, 1995, Bertell, 1995).

The calculation of risk estimates have been largely derived from populations which have been exposed to high doses of radiation over relatively short periods of time. However, the

extrapolation of risks from one population to another is fraught with problems, even in the absence of sampling variability and bias. As BIER V (1990) point out, the method of such extrapolation depends on the mathematical model selected; and although empirical evidence may be available from studies carried out on both populations, there is often considerable uncertainty about the validity of the procedure used.

Summary

Most of the studies discussed in subsequent sections of this report have been criticised for, and indeed have acknowledged, the existence of one or more major methodological limitations such as those discussed above. This does not mean, however, that the results of this research must be dismissed out of hand, rather the findings must be considered in light of these difficulties, and interpretations and generalisations of data must be made with caution. Given the inherent difficulties in undertaking research of this nature, the findings from published studies to date provide us with, at least, indications of possible radiation effects in participant veterans and with directions for future research.

The U.K. programme of atmospheric nuclear weapons testing included a series of 9 operations from Hurricane in 1952 to Grapple Z in 1958. The involvement of New Zealand military personnel in that programme has been detailed (Crawford, 1989) and summarised (Pearce, et al., 1990) elsewhere, this report provides a brief description only.

New Zealand personnel played minor roles in Australian-based tests but the primarily involvement occurred as part of Operation Grapple. The operation involved the detonation of 3 H-bombs in the Vicinity of Malden Island during May and June 1957 and a further 4 H-bombs and 2 atomic bombs at Christmas Island between November 1957 and September 1958. Two RNZN frigates, HMNZS Pukaki and Rotoiti acted primarily as weather ships with secondary tasks such as the provision of air/sea rescue, anti-submarine surveillance, thermal flash monitoring, and water sampling (Crawford, 1989). The frigates were stationed at varying distances of between 20 to 150 nautical miles from ground zero throughout the series of tests. However, Pukaki passed within 6 nautical miles of ground zero approximately 5 to 6 hours following Grapple 1, and passed through ground zero a day after Grapple Y (Crawford, 1989).

Official reports indicate that the degree of precaution exercised and use of protective clothing declined with successive tests, apparently because of the absence of significant radiation (Crawford, 1989). Although external radiation was monitored with the use of personal film badges, data from the badges are unavailable and official documentation provides little evidence of post-test radiation above very low levels. However, the accuracy of the recording of the official data, and other points, has been disputed by some of those who participated in the tests (e.g. Gulbransen, 1989; Rimpac, 1997).

In the late 1970s the Centers for Disease Control (CDC) undertook a study which examined the health status and causes of death among veterans exposed to ionizing radiation at the Nevada test site during the 1957 "Smoky" test. A preliminary report of the findings indicated an increased incidence of leukaemia among 3224 exposed veterans (Caldwell et al., 1980). However, the report was based on findings for only 76% of all Smoky participants. An extended report presented findings for 3072 (95.5%) test participants for the follow-up period 1957 to 1979 (Caldwell et al., 1983). Overall mortality, cancer mortality and cancer incidence was lower than expected on the basis of U.S. national figures. Consistent with the preliminary report, the data showed a statistically significant increase only for leukaemia incidence and mortality (Caldwell et al., 1983).

The authors acknowledged that the study suffered from a poorly defined cohort and incomplete exposure data, and the study has been criticised for the use standardized mortality ratios without addressing the "healthy soldier effect" (Roff, 1997). In view of the lack of significant increase in either the incidence or mortality from any other radiogenic cancers and an apparent lack of dose effect by unit, the authors concluded that the findings on leukaemia were attributable "either to chance, to factors other than radiation, or to some combination of risk factors which may include radiation" (Caldwell et al., 1983, p. 620). It has also been noted that although the SMOKY test was the highest-yield tower shot conducted at the Nevada Test Site, the recorded doses for SMOKY participants as a group were too low to explain the excess, and the question of whether it represents a random event, an underestimation of the doses for the few participants who got leukaemia, or some other explanation still requires clarification (ACHRE, 1995).

The findings from the CDC research prompted a study by the National Academy of Science (NAS) Medical Follow-up Agency (MFUA) which sought to determine whether the findings for Smoky participants were unique to that test. An extensive study of participants from five test sites was conducted to investigate if health was adversely affected by participation (Robinette et al., 1985). MFUA subsequently learnt that there were errors in the Defence Nuclear Agency (DNA) supplied data, which formed the basis for their analyses. An estimated 15,000 names were mistakenly omitted from the study roster and approximately 4,500 names were incorrectly included (MFUA, 1996).

In addition to the data problems, the study has been criticised for inappropriate statistical analyses, in particular the use of SMRs as the sole risk comparison. Critics have also argued that in the absence of a nonparticipant control group, the study could not address the "healthy soldier effect" (Bullman & Kang, 1994). Although the effect was discussed in the original report and a method of correcting it was described, Bross and Bross (1987) argue that false negative results were reported because no correction was actually made. Accusing Bross and Bross of gerrymandering the data to support preconceived ideas, the authors of the MFUA report took issue with the criticisms, and were not persuaded by the their arguments or by the findings from their "corrected" analyses (Jablon, 1987).

In light of the data problems, the published results were withdrawn from discussion pending a reexamination and correction of the data and MFUA is currently undertaking an updated "Five Series Study" with appropriate modifications. The results of the revised study are not expected before 1998 (MFUA, 1996).

In 1987 findings were reported from a study of mortality of Canadian military personnel exposed to low-level radiation (Raman, 1987). The exposure occurred during nuclear reactor

clean-up operations at the Chalk River Nuclear Laboratories (1953 and 1958) or during atmospheric nuclear weapons testing in Nevada and Australia (1955 to 1957). A comparison between 954 exposed subjects and 1,908 matched controls showed little variation in overall mortality or cause-specific mortality between the groups. The only significant difference was that mortality from all diseases of the digestive system, particularly from cirrhosis of the liver, was significantly higher in the exposed group. However, the authors suggested that these findings were most likely a statistical artefact due to multiple comparisons, as 171 were made in all (Raman et al., 1987).

Using SMRs for comparability with previous studies, Raman et al. (1987) reported that mortality rates for cancer of the oesophagus and for suicide were significantly higher in the exposed group than was expected from national death rates, however there were no significant differences in the frequency for either cause of death between the exposed and control groups. Analyses by estimated radiation dose, based on film badge readings, also failed to show any significant associations. As the authors not, this is hardly surprising given the very low doses recorded, and given the poor quality of dose information (Raman et al., 1987).

A year later the National Radiological Protection Board (NRPB) reported findings from a study of the health status of men who participated in the UK atmospheric nuclear weapons tests and experimental programmes that took place in Australia and the Pacific Ocean between 1952 and 1967 (Darby, et al., 1988). Comparisons between 22,347 test participants and 22,326 matched military controls showed that total mortality and mortality from all neoplasms combined were almost identical in both groups. When data was examined for 38 causes of death separately, mortality rates from leukaemia, multiple myeloma, and other injury and poisoning were found to be higher in test participants compared to controls, and rates for

cancers of the prostate and kidney and chronic bronchitis were significantly lower in test participants (Darby, et al., 1988).

Darby et al. (1988) concluded that there was no detectable effect of participation on life expectancy or the risk of developing cancer, apart from a possible effect on the risks of developing leukaemia and multiple myeloma. The apparent differences between participants and controls were interpreted as due to chance, and perhaps to some differences in smoking habits (Darby et al., 1988). A subsequent study which extended the follow-up period by an additional 7 years examined the health status of 21,358 (85%) participants and 22,333 matched military controls (Darby et al., 1993a).

During the additional 7-years of follow-up, mortality from all-causes, all neoplasms, leukaemia, and multiple myeloma were lower than expected on the basis of national data. Mortality rates varied little between test participants and controls (Darby et al., 1993a). The report, however, focused on the period more than 10 years after the initial test participation. Analyses for this period showed that mortality rates for all neoplasms and for all other causes of death were lower than expected on the basis of national data (Darby et al., 1993a). The relative risk for participants compared with controls was near unity for all-causes and all neoplasms; was raised for cancer of the bladder and for leukaemia, and; was significantly less than unity for cancers of the mouth, tongue and pharynx and for lung cancer (Darby et al., 1993b).

In terms of incidence, there was no significant difference between participants and controls for all neoplasms, but tests participants had significantly higher rates of liver cancer, cancer of the bladder, and leukaemia, and; significantly lower rates of non-melanoma skin cancer (Darby et al., 1993b).

The failure to support the previous findings of a higher risk for leukaemia and multiple myeloma in test participants (Darby et al., 1988) led the authors to suggest that the initial findings were due to a chance occurrence of low rates in the control group. Although they were unwilling to dismiss the possibility that test participation may have caused a small risk of leukaemia in the early years after the tests, Darby et al. (1993a) concluded that participation in the nuclear weapons testing programme had not had a detectable effect on participants expectation of life nor on their risk of developing cancer or other fatal diseases. In a thorough critique of the NRPB studies, Roff (1977) raised a number of important methodological issues and argued that the research is flawed. A discussion of these and other limitations can be found in the following summary of the NRPB research.

Similar findings were reported from a study of New Zealand participants of Operation Grapple, a series of U.K. atmospheric nuclear weapons tests conducted at Christmas and Malden Islands during 1957 and 1958 (Pearce, et al., 1990). The study included 528 Navy participants of the operation and 1504 non-participant Navy controls. Follow-up for the period 1957-1987 was 94% complete for test participants and 91% complete for controls.

A comparison of total mortality between test participants (70 deaths) and controls (179 deaths) showed a very small increase in risk among participants. When compared to national data both groups had higher rates of cancer mortality, an elevation which Pearce et al. (1990a) suggested may be due to high rates of smoking. There was a modestly elevated risk of cancer mortality in test participants compared to controls which was not significant. While there was little evidence of an increased risk of non-haematological cancer mortality or incidence among participants, there was an increased risk for haematological cancer mortality and incidence, particularly for leukaemia.

Pearce, et al. (1990) noted that their findings for leukaemia were similar to those reported by Darby et al (1988) and similarly acknowledged that some leukaemias, and possibly some other haematological cancers, may have resulted from test participation. They cautioned, however, that their results were based on a small number of observations. They concluded that participation in Operation Grapple did not result in a detectable increase in mortality from causes other than cancer; that there was little evidence of an increased risk for non-haematological cancers and; that there had "not been a detectable effect on overall life expectancy from participation in the programme" (Pearce et al., 1990b, p.1165).

A supplementary report by Pearce et al. (1996) presented findings for an extended follow-up of a further five years. In total, 97 participant and 256 control deaths were recorded for the entire 1957-1992 follow-up period. The additional data showed no significant difference between test participants and controls for risk of death from causes other than cancer. Consistent with the initial report was the finding of increased mortality and incidence rates among test participants for all haematological cancers and for leukaemia in particular.

The authors concluded that the evidence remained consistent with the hypothesis that some leukaemias and other haematologic cancers may have resulted from participation in the nuclear weapons testing programme, and maintained that the extended follow-up strengthened the evidence that there was "no increased risk for non-haematologic cancers or for causes of death other than cancer in the test participants" (Pearce et al., 1996; 1997).

Watanabe et al. (1995) also undertook a study of the mortality of Navy atmospheric test veterans. The study involved 8554 U.S. Navy personnel who participated in Operation Hardtack I in the Pacific (1958), and a control group of 14,625 Navy veterans who did not participate in any nuclear tests. Vital status data recorded for the follow-up period (1958-

1991) identified 12.7% of participants and 11.6% of controls as deceased. Unadjusted rate ratios showed that among Hardtack participants there was a significant excess in all-causes mortality, and while there was no significant difference in all-cancers mortality, the number of deaths from cancer of the digestive organs was significantly higher in Hardtack participants compared with controls. After adjustment for military rank cancer of the digestive organs continued to be significantly elevated among participants.

On the basis of individual radiation exposure dose estimates, Hardtack participants were categorised into 3 groups. Significant relative risks were observed for all-cause, all-cancers, and liver cancer in the high dose group (>1000 mrem); for pancreatic cancer in the medium dose group (251 - 1000 mrem); and for cancer of the digestive organs in the low dose group (0 - 250 mrem). The authors concluded that, despite the lack of evidence for elevated rates of suspected radiogenic cancers among the Hardtack participants, the possibility that they may be at an increased risk of death from certain cancers could not be dismissed (Watanabe et al., 1995).

In addition to the "Five Series Study", MFUA also conducted a study of the mortality experience of naval participants of the U.S. atmospheric nuclear weapons tests in the Marshall Islands in 1946 (Operation Crossroads). Using proportional hazards analysis, the study compared the mortality experience of approximately 40,000 Naval personnel who participated in Crossroads with that of a matched control group of military personnel who had not participated in the operation. Crossroads participants were found to have a significantly higher mortality than nonparticipating controls but there were no significant differences found for mortality from all malignancies or leukaemia. There were no statistically significant increases found for mortality in any of the 44 specific cancers and diseases examined in the study (MFUA, 1996).

Because available radiation exposure data were not considered suitable for analysis, the study used exposure surrogate groups, including "participation" status as a general proxy for exposure (MFUA, 1996). "Boarders" of target ships and "Engineering and Hull" (E&H) occupational specialists were used as high exposure surrogate groups. Mortality due to all malignancies and leukaemia did not vary substantially among the groups. While both boarding and nonboarding participants had significantly higher all-cause mortality than nonparticipating controls, the risk to boarders was not significantly different from nonboarders. Aside from all-cause mortality, risks for boarding participants did not significantly exceed those for controls for any of the disease categories, and were similar for boarding and nonboarding participants. There were no significant differences recorded in mortality from any cause between the E&H and non-E&H participants, or between either of these groups and the non-participant controls (MFUA, 1996).

The Crossroads researchers concluded that "the findings do not support the hypothesis that exposure to ionizing radiation was the cause of increased mortality among Crossroads participants". Rather, it was suggested that the elevated risk of all-cause mortality in Crossroads participants was probably the result of two factors: an unidentified factor (other than radiation) associated with participation in, or presence at, Operation Crossroads; and a self-selection bias within the participant roster (MFUA, 1996).

From a review of studies concerned with the psychological effects of invisible environmental contaminants, Vyner (1988a) suggested that exposure can cause the development of adverse psychological effects amongst exposed individuals. The adverse psychological effects of such contaminants, he maintains, are revealed as experienced uncertainty, adaptational dilemmas, hypervigilence, nonempirical belief systems about the exposure, and traumatic neurosis (Vyner, 1988a). Furthermore, he suggests that there is a syndrome recognisable among

veterans which includes: a belief that they will die prematurely, and from a disease caused by radiation; a disrespect for the medical professional generally, but a desire to find the one doctor with the answers; anger at the government, and guilt over that anger; a heightened concern for the future generations; a belief that they wee used as guinea pigs, a willingness to serve in the military again, but a refusal to be involved again with nuclear weapons; and a belief that people think they are crazy for their beliefs about ionizing radiation. The "syndrome" may result in a preoccupation with health and radiation and a series of identity conflicts (1988b).

Also concerned with the psychological effects of exposure, Murphy, Ellis, and Greenberg (1990) presented data from in-depth interviews of 7 atomic veterans and their families. Participants were selected from the NAAV mailing list. Within the variation of the interview data some common themes emerged, the most prominent being the invalidation of veterans' experiences by authority figures. Veterans and spouses with children expressed concerns about passing on genetic effects to future generations, and the remaining themes related to a desire among family members to protect each other from their fears of physical consequences and the desire of veterans to leave a record of their experiences to help prevent future suffering (Murphy, et al., 1990). While the authors acknowledged that the generalizability of the research findings are limited by the nature of the small, unrepresentative, and self-selected sample, they concluded that the study indicated "powerful psychological effects on all family members from exposure to low-level ionizing radiation".

A similar study was undertaken by Garcia (1994) in which she explored the memories and perceptions of radiation exposure in interviews with 16 atomic veterans. Participants in this study were also selected from the NAAV mailing list. The data led Garcia (1994) to the conclusion that atomic veterans are faced with "reconciling a belief in their country with

experiences of a lack of government attention to their safety and with unsuccessful efforts to obtain health benefits for radiation-related illnesses" (p.654). Resolution, it was suggested, involves the emotional and cognitive processing a new perspective of the experience that contradicts their prior beliefs (Garcia, 1994). Several aspects of this "emotional work" were noted: feelings of ineffectiveness and helpless in the face of a potent, unresponsive government; feelings of ambivalence about anger with a significant life symbol and the lack of role models, and; a sense of isolation from other atomic veterans and consequent intensification of self-doubt (Garcia, 1994).

Adelstein (1987) agrees that for many the long-term consequences of exposure are frightening, and suggests that the perception of risk is contextual. The fear of radiation received from a nuclear accident, for example, is thought to be greater than the fear of threat from natural and medical sources (Adelstein, 1987). Some of the features that separate risks in terms of public perception and acceptability include the degree to which the exposure is deemed to be voluntary, the immediacy and reversibility of risk, and aspects of the perceived cause of the exposure, such as whether it is occupation-related, naturally occurring, or necessary.

A chief concern expressed by atomic veterans is the fear of radiation-related genetic effects on their families (Murphy, Ellis, & Greenberg, 1990; NZRSA, 1996), however, none of the studies reviewed thus far have assessed reproductive effects. At the request of the Department of Veterans Affairs the MFUA established a committee to study the feasibility of epidemiologic studies of adverse reproductive outcomes in the families of atomic veterans (MFUA, 1995). The Committee's assessment was that there are insurmountable difficulties, including: finding and contacting a sufficiently large number of study subjects (offspring of atomic veterans); establishing an accurate measure of dose for each veteran; detecting the extremely small potential risk at low doses; identifying and reliably documenting reproductive

outcomes over time; and measuring other potentially confounding factors that have been observed to cause reproductive problems. They conclude that as a result of the difficulties, which become even greater in the grandchildren of the veterans, a scientifically accurate and valid epidemiologic study of reproductive problems among the families of atomic veterans is not feasible (MFUA, 1995).

Summary

The primary focus of atomic veteran research has been the examination of mortality rates and causes. While the use of SMRs with this veteran cohort has been criticised, most studies have utilised some form of proportionate analysis, even if only for comparison with previously reported findings. A range of SMRs have been reported for overall mortality in participants or exposed personnel which suggest that the mortality rate for this cohort does not differ significantly from national mortality rates.

Findings for participant cancer mortality are inconsistent with reports of both higher and lower SMRs (Darby et al., 1993a; MFUA, 1996; Pearce, et al., 1990). In terms of specific cancer sites, higher rates of participant mortality have been reported from cancers of the prostate (Watanabe et al. 1995) and leukaemia (MFUA, 1996). However, Darby et al. (1993a) reported that mortality from leukaemia and multiple myeloma were lower than expected on the basis of national data.

More reliable data is derived from direct comparisons of the mortality rates for participant and control groups. Data from a range of studies suggest that overall mortality and mortality from all-cancers varies little between these groups (Darby, et al., 1998; 1993a; Pearce, et al. 1990; 1996; Raman, 1987). In contrast, Watanabe et al. (1995) found a significant excess in all-cause mortality among Hardtack participants compared to controls. Similarly, Crossroads

participants had significantly higher all-cause mortality than non-participants, yet there were no significant increases for mortality in any of the 44 specific cancers and diseases examined in that study (MFUA, 1996).

In contrast, all other studies that examined the rates of cause-specific mortality found at least one significant excess or deficit in participant rates when compared with controls. The data from the NRPB studies showed statistically significant increases for leukaemia and multiple myeloma in test participants (Darby et al., 1988). Subsequent analyses for the period more than 10 years since participation confirmed the elevated risk of leukaemia mortality in participants, but also found an increased risk of mortality from cancer of the bladder (Darby et al. 1993a). In the same period, participants had lower relative risks for cancers of the mouth, tongue and pharynx and for lung cancer (Darby et al. 1993a). Consistent with the findings of Darby et al. (1988; 1993) the New Zealand data showed an increased risk among participants for mortality from haematological cancer, in particular from leukaemia (Pearce, et al., 1990; 1996). In the Canadian sample the only significantly elevated risk for exposed personnel was for death from diseases of the digestive system, particularly cirrhosis of the liver (Raman, 1987). Similarly, Hardtack participants recorded significantly higher mortality from cancer of the digestive organs compared to non-participants (Watanabe, et al. 1995).

Only three of reviewed studies reported incidence data. The CDC study, which did not include a control group, compared participant incidence rates with national rates. The results showed that while the overall incidence of cancer was lower, the incidence of leukaemia was significantly higher in participants (Caldwell et al., 1983). Darby et al., (1993b) reported that while there was no significant difference between participants and controls in the incidence of all neoplasms, test participants had significantly higher rates of liver cancer, cancer of the bladder, and leukaemia, and that they had significantly lower rates of non-melanoma skin

cancer (Darby et al., 1993b). Pearce et al. (1996) found no evidence of an increased risk of non-haematologic cancer incidence among participants but reported increased incidence rates among test participants for combined haematological cancers and for leukaemia in particular (Pearce et al., 1990; 1996).

Given the limited extent of incidence data for veteran samples, and despite the dangers inherent in extrapolation of risks from one population to another, it may be helpful to consider the findings reported from A-bomb survivor studies. Recent research findings relating to this cohort are reviewed briefly in the following section. In the "Life Span Study" (LSS) cohort, a significant excess risk has been reported for all solid cancers, and for cancers of the stomach, colon, lung, breast, ovary, urinary bladder, thyroid, liver, non-melanoma skin cancer (Thompson et al., 1994), and cancer of the salivary gland (Land et al. 1996; Saku et al., 1997; Thompson et al., 1994). No evidence was found for increased risk of cancers of the oesophagus, rectum, gallbladder, pancreas, larynx, uterine cervix, uterine corpus, prostate, kidney, renal pelvis, or oral cavity and pharynx as a group (Thompson et al., 1994).

Strong evidence of radiation-induced risks for acute lymphocytic leukaemia, acute myelogenous leukaemia, and chronic myelocytic leukaemia have also been reported (Preston et al. (1994). However, the same study found no evidence of excess risk for adult T-cell leukaemia or multiple myeloma, and few cases of chronic lymphocytic leukaemia were observed (1994). When the incidence of 19 nonmalignant disorders was examined, Wong et al. (1993) detected a significant excess risk for uterine myoma, chronic liver disease and cirrhosis, and thyroid disease (i.e. the presence of one or more noncancerous thyroid conditions).

In 1983 the U.K. Ministry of Defence commissioned the National Radiological Protection Board (NRPB) to undertake a study of the health of participants of the UK atmospheric nuclear weapons tests and experimental programmes that took place in Australia and the Pacific Ocean between 1952 and 1967. Using Ministry of Defence records, 22,347 test participants were identified and 22,326 matched controls were selected.

Comparisons were made between the two groups on mortality and cancer incidence rates, as determined from death certificates and national records of cancer registration. The number of deaths observed were also compared with national mortality rates (Darby et al., 1988).

Total mortality and mortality from all neoplasms combined were almost identical in test participants and controls. An examination of the data for 38 separate causes of death showed that mortality from leukaemia, multiple myeloma, and other injury and poisoning, was significantly higher in participants compared to controls, but mortality rates for cancers of the prostate and kidney and chronic bronchitis were significantly lower.

The authors concluded that test participation had no detectable effect on participants' expectation of life or their total risk of developing cancer, apart from a possible effect on the risks of developing leukaemia and multiple myeloma. The evidence was deemed to be confusing and the differences observed between participants and controls were interpreted as due to chance, and perhaps to some differences in smoking habits (Darby et al., 1988).

Further follow-up.

A subsequent study was undertaken which extended the follow-up by a further 7 years (Darby et al., 1993a). Again, using Ministry of Defence records, 21,358 personnel were identified as having participated in U.K. nuclear weapons tests at Monte Bello Island, Emu Field and Maralinga Range in Australia and at Malden and Christmas Islands in the Pacific Ocean. This group included those studied previously plus a few additional test participants located in archival records, but excluded 1503 men judged to have had no more likelihood of exposure to radiation from the tests than members of the general public (i.e. personnel who visited test sites but left before the first detonation). In addition, a group of 22,333 men who had not participated in the tests were also identified from Ministry of Defence records as matched controls. Radiation exposure data was drawn from information from film badges issued at the tests and which was made available by the Ministry of Defence for 5686 men.

Summary of major findings

Follow-up period: A further 2488 deaths were recorded during the seven year follow-up period, during which time mortality was lower than expected on the basis of national rates for all-causes (SMR = 0.86), all neoplasms (SMR = 0.85), leukaemia (SMR = 0.57), and multiple myeloma (SMR = 0.46) (Darby et al., 1993a). Mortality rates varied little between test participants and controls for the same causes (RRs 0.99, 0.96, 0.57, and 0.57 respectively; 90% CI all included 1.00) (Darby et al., 1993b). In terms of the two major smoking-related diseases, the incidence of lung cancer continued to be somewhat less frequent in test participants compared to controls (RR = 0.93, 0.76-1.13), whereas mortality from bronchitis, emphysema, and chronic obstructive lung disease was significantly greater in test participants than in controls (RR = 1.57, 1.05-2.34) (Darby et al., 1993a).

Long-term health effects: An examination of the mortality data by broad cause of death showed that mortality from all causes, from all neoplasms, and from all other diseases was substantially lower in both groups than national figures, but mortality from accidents and violence was higher. Very little difference was observed between the experience of the test participants and the controls (Darby et al., 1993a). Further examination of the data for different periods after the start of test participation showed that for all neoplasms and all other diseases, mortality in comparison with that expected from national rates was exceptionally low in the first 10 years (SMRs 0.72 and 0.54, respectively).

Arguing that any effect of test participation on the incidence of neoplasms other than leukaemia is likely to be concentrated in the period more than 10 years after the start of test participation, and in an attempt to address the healthy soldier latency issue, evidence for long-term effect of test participation was sought after excluding the first 10 years of observation (Darby et al. 1993a). After this exclusion, the necessity and legitimacy of which has been queried (Roff, 1977), the mortality among test participants remained low for all neoplasms (SMR = 0.84) and for all other causes of death (SMR = 0.82) and rates in test participants and controls remained very similar (RR = 0.97 (0.91-1.04) for incidence of all neoplasms, and RR = 1.02 (0.96-1.08) for mortality from all causes of death other than neoplasms).

In the period more than 10 years after the initial test participation, rates were examined for a total of 41 different causes of death. Based on the contention that radiation related increases in leukaemia usually reach a maximum within five years of exposure, this data was considered for the entire follow-up period and for 2-25 years after initial test participation (Darby et al., 1993a).

The relative risk for participants compared with controls was near unity for all causes (0.99, 0.95-1.04) and all neoplasms (0.95, 0.87-1.04) and significantly greater than unity for cancer of the bladder (2.69, 1.42-5.20), and for leukaemia (whole follow-up: 1.75, 1.01-3.06; 2-25 years: 3.38, 1.45-8.25). The relative risk was significantly less than unity for cancers of the mouth, tongue and pharynx (0.45, 0.22-0.93) and for lung cancer (0.85, 0.73-0.99). For the remaining cancers, including multiple myeloma, death rates in participants and controls were similar in all cases except for liver cancer (Darby et al., 1993b). According to Darby et al., (1993a) this is the number of significant differences which could be expected to occur by chance, and moreover they contend that the significant excesses of bladder cancer and liver cancer may be largely due to the unusually low rates among the controls.

When the analysis was repeated for cancer incidence, there was no significant difference in the incidence of all neoplasms between participants and controls (RR = 0.97, 0.91-1.04). Individual cancer types with significantly higher incidence rates in tests participants than in controls were liver cancer (2.89, 1.11-7.94), bladder cancer (1.45, 1.03-2.03), and leukaemia (whole follow-up: 1.61, 1.00-2.57; 2-25 years: 3.45, 1.72-7.10). The relative risk for non-melanoma skin cancer was significantly lower in participants than in controls (0.77, 0.63-0.95), and while somewhat different rates were observed for lung cancer and tumours of the central nervous system, these did not quite reach statistical significance (Darby et al., 1993b).

Analyses by recorded radiation dose or type of test participation failed to indicate any specific hazard. However, the adequacy of exposure data which was derived from film badge information must be questioned.

Conclusions

Darby et al. (1993a) concluded that participation in the nuclear weapons testing programme had no detectable effect on participants' expectation of life nor on their risk of developing cancer or other diseases. They argued that the findings of higher risk for leukaemia and multiple myeloma found previously in test participants (Darby et al., 1988) were not supported in the follow-up study, suggesting that the previous findings were due to the chance occurrence of low rates in the control group. Similarly, they maintained that the excess of leukaemia in test participants compared with controls in the period 2-25 years after the tests was likely to be a chance finding. However, they were unwilling to rule out the possibility that test participation may have caused a small risk of leukaemia in the early years after the tests (Darby et al., 1993a). They also concluded that the suggestions from the previous study that participants may have smoked less than the controls and so experienced lower rates of smoking-related diseases were not supported by the later data and were, therefore, also likely to be chance findings.

Methodological issues

In an thorough critique of the NRPB studies, Roff (1977) raises a number of important methodological considerations and argues that the research is flawed. In terms of the validity of the control group, she notes that it may have been drawn from men who were in fact exposed to residual radiation by being within range of fallout, by entering a test zone during a period of residual radiation, or by serving on or using equipment which had been irradiated (Roff, 1977). Although there was no comprehensive list of participants compiled at time of the U.K. tests, Darby et al. (1993a) contend that after extensive searching of Ministry of Defence records, 85% of eligible men were included in the study. This raises the issue, however, of the possibility for differential selection amongst the 15% not included.

With regard to the finding of significantly elevated levels of leukaemia in test participants, Darby et al (1993a) argued that "the excess over the controls seems likely to be attributable principally to a deficit in controls, since the mortality in the controls was atypically low..." Such reasoning, Roff (1997) argues, would appear to presume much of what the study purported to be about and would seem to undermine the very rationale of using a control group. Similarly, the Advisory Committee on Human Radiation Experiments suggest that the interpretation difficulties are problematic and remain unresolved (ACHRE, 1995).

The exclusion of the 1503 men judged to have had no more potential of exposure to radiation than members of general public is also problematic. According to the authors, the harmful effects associated with the tests could be obscured by including as participants men who were only peripherally involved. Supplementary data provided in an appendix shows elevated risks of liver cancer and leukaemia which follow broadly the trends in test participants (Darby et al., 1993a). While they argue that this was to be expected if the elevated risk in the participants was due principally to unduly low rates in the controls, Roff (1997) suggests that it may also indicate a similar pattern because of similar exposure for the 1502 excluded men.

Roff (1997) also notes that while the deaths from external causes fell during the last seven years of the study, there was a marked rise in those conditions of longer latency. A reexamination of the data shows that there were almost as many deaths from neoplasms recorded in the last 7 years as in the first 31 years, including three times as many deaths from cancers of the prostate and cancer. The significance of these findings, she contends, is obscured by the use of SMRs uncorrected for the healthy soldier effect.

As noted previously, Roff (1997) contends that the of SMRs to establish relative risks is bound to result in an underestimation of relative risk. She points out that 709 cancer deaths

were observed among the participants and 787 cancer deaths were observed among the controls - a difference in sample sizes of 11%. After correcting the data for the difference, she maintains that a very different pattern of excess mortality is shown for test participants which suggests "a consistent pattern of heightened risk for site specific cancers known to be radiogenic for veterans who were exposed to fallout in the Pacific Proving grounds and the Australian test sites (Roff, 91997, p.81)."

New Zealand participants of Operation Grapple

There has been only one published study concerned with the health of New Zealand participants of atmospheric nuclear weapons testing. The study, commissioned by the Ministry of Defence (MOD), sought to investigate mortality and cancer incidence in a group of New Zealand military personnel known to have participated in the atmospheric nuclear weapons tests conducted by the United Kingdom at Christmas and Malden Islands during 1957 and 1958 (Pearce, et al., 1990a).

The general study design involved ascertaining subsequent deaths and cancer incidence in RNZN personnel who participated in Operation Grapple aboard the HMNZS Pukaki and Rotoiti during 1957-1958. These personnel were identified from navy service records and annual navy lists of officers (1990b). A comparison group was also identified which consisted of regular RNZN personnel serving on HMNZS Lachlan, Royalist and Kaniere which were in service during 1957-1958, but were not involved in Operation Grapple. Both groups were primarily selected from MOD records, however a complete list of test participants was not available. After validation from independent sources, and exclusion on the basis of ineligibility (e.g. conscripts) or missing data, 528 test participants and 1504 controls were identified for inclusion in the study. In an attempt to confirm vital status information and data from MOD records, and to collect new information (such as smoking behaviour), a brief postal questionnaire was sent to all subjects believed to be alive and for whom a current address could be attained. Follow-up was carried out for the period 1957 to 1987 and was 94% complete for participants and 91% complete in the controls (1990a).

Mortality data was gathered from records at the Justice Department and National Health Statistics Center, cancer incidence data was gathered from the records of the New Zealand

Cancer Registry. Using essentially the same coding rules as those employed by Darby et al (1988), subjects were recorded as having only one type of cancer, because of the difficulties of distinguishing multiple independent primary cancers from single tumours recurring at multiple sites.

Summary of major findings

There were 70 deaths among test participants (SMR=1.15), 179 deaths among the controls (SMR=1.06) and there was a slight deficit for death from non-cancer causes for both test participants (SMR=0.95), and controls (SMR=0.99). There were no significant differences between the groups for all-cause or for non-cancer mortality with all relative risk findings falling within the range of normal statistical variation (Pearce, et al., 1990a).

Both test participants and controls had elevated cancer mortality when compared to national data (SMRs = 1.80 and 1.30 respectively). A modestly stronger elevation of risk in test participants compared to controls was not statistically significant. The mortality rates for 16 non-haematological cancer sites were examined, however, many of the comparisons involved very small numbers and the relative risk estimates were therefore unstable. The overall relative risk for non-haematological cancer mortality was not significant. There was a significant excess of deaths from haematological cancers among test participants (7) compared to controls (RR = 3.25, 1.12-9.64, p = 0.02), 4 of which were from leukaemias (RR = 5.58, 1.04-41.6, p = 0.03). There were no deaths from multiple myeloma in the test participants, but the expected mortality was only 0.2 (Pearce, et al., 1990a).

Similar findings were reported for cancer incidence which was examined for 12 specific sites. There were no significant differences between participants and controls for cancer incidence overall, for cancers other than haematological malignancies, or for haematological cancers.

There were no cases of multiple myeloma in the test participants, but the expected mortality was only 0.3. The relative risk for incidence of leukaemia, however, was 5.51 (1.03-41.1, p = 0.03) (Pearce, et al., 1990a).

Conclusions

The authors concluded that "New Zealand participants in the British nuclear weapons test programme have not experienced any detectable increase in risks of death for causes other than cancer, and there is little evidence of an increased risk for non-haematological cancers" and that there has not been a detectable effect on overall life expectancy from participation in the programme" (Pearce et al., 1990b, p. 1165). While they acknowledged that some leukaemias, and possibly some other haematological cancers, may have resulted from test participation, they cautioned that the results were based on small numbers.

Further follow-up.

A supplementary report presented findings for an extended follow-up of a further five years from 1988-1992 (Pearce et al., 1996). During the additional follow-up study there were 9 more participant deaths and a further 77 deaths in the controls, giving 97 participant deaths and 256 control deaths for the entire 1957-1992 follow-up period. Non-cancer mortality was similar for both groups and cancer mortality was slightly, but not significantly, elevated in participants. While the relative risk for death from non-haematological cancers reached unity, there were 8 deaths from haematologic cancers in test participants compared with 6 in the controls (RR= 3.8, 1.4-10.8). Again, the excess was due mainly to the 4 participant deaths from leukaemias (RR = 5.6, 1.0-41.7).

During the additional follow-up period cancer registrations increased by 13 among test participants and by 47 in the controls, yielding a relative risk of 1.0 (0.8-1.4) for cancer

incidence. Relative risks for specific cancer sites were 1.0 (0.7-1.30) for non-haematological malignancies, 1.9 (0.8-4.3) for haematologic cancers, and 5.6 (1.0-41.6) for leukaemia.

Conclusions

On the basis of these findings, Pearce et al. (1996; 1997) concluded that the evidence was still consistent with their hypothesis that some leukaemias and other haematologic cancers may have resulted from participation in the nuclear weapons testing programme. They also maintained that the further follow-up strengthened the evidence that there was no increased risk for non-haematologic cancers or for causes of death other than cancer in the test participants.

Methodological issues

Certain methodological concerns arise from the Pearce et al. studies, particularly in relation to the definition of the study cohort and validity of the control group. Questions have been raised as to the completeness of the participant group (Rimpac, 1997), and it has been argued that the control group may have included men who were in fact exposed to residual radiation (Roff, 1997, Rimpac, 1997). Pearce et al (1990) claim that the control group comprised regular RNZN personnel serving on HMNZS Lachlan, Royalist and Kaniere during the same period but who did not participate in the weapons tests. According to Roff (1997), however, it is not certain that the ships, or the controls, never entered the test zones during the period of residual radiation, or were not exposed to fallout (Roff, 1977).

The possibility of bias due to the omission of some participants is noted by Pearce et al. (1990b) as the least satisfactory aspect of the study. They argue, however, that such a bias would be expected to affect all causes of death, not only haematological cancers, and thus, it seems unlikely that observed differences can be accounted for by such a bias. Comparing

the situation to that of the NRPB studies, Pearce et al contend that the problem of "omission bias" was less likely to affect the New Zealand study because of the comparative rates of omission: 5% in case of their study, 17% in NRPB study (Darby et al., 1993b).

Another criticism levelled at the Pearce et al study relates to the use of SMRs to calculate relative risk. The expected number of deaths were calculated by multiplying the national mortality rates by the person-years at risk in each category of age and calendar year. For each outcome, the observed mortality was then divided by the expected mortality to yield the SMR. The relative risk for each outcome was then estimated taking the SMR in the test participants and dividing it by the SMR in the controls. Pearce et al (1990a) acknowledged the dangers of such an approach, but maintained that the problem was trivial when, in the study, the age and calendar period distributions of the two groups were similar.

Roff (1977) contends that crude SMR/RRs calculated in this manner are bound to underestimate the relative risk since "528 exposed men are compared with 1504 (presumably) unexposed men - a difference in sample size of 35.10% " (p. 9). She goes on to argue that if the 70 participant deaths are compared with 35.10% of the 179 deaths among the controls (i.e. 70:62.82), the RR would be 111, an 11% increase in crude death figures among the participants.

Pearce et al. (1997) not that greatest problems of interpretation of findings apply to those for leukaemia and other haematological cancers. Three explanations, apart from chance were suggested: bias, confounding, or casual relationship. Although others are likely to disagree, they argue that serious bias in unlikely to have occurred in the study design, and that the existence of a confounding variable in the study is unlikely given test participants and controls were similar in most respects (Pearce et al., 1997).

In relation to the findings of the increased risk of leukaemia, Pearce et al (1997) also noted the criticism that the latency period was too long (3 of the 4 leukaemia occurred more than 25 years after the tests) (Pearce, et al., 1996). Although they acknowledge that the latency period between exposure and diagnosis of ionizing radiation induced leukaemia is about 2-25 years, they also note that longer latency periods have been reported in Hiroshima survivors aged less than 35 at the time of exposure. Therefore, they argued, the leukaemia findings could not be dismissed simply on the basis that some leukaemias were diagnosed more than 25 years after test participation (Pearce, et al., 1996). The possibility of diagnostic bias, that leukaemias were more readily diagnosed because of their known association with radiation, was also noted.

Finally, the authors noted the absence of reliable radiation exposure data for New Zealand Operation Grapple participants, and acknowledged the possibility of internal radiation exposure since the Pukaki and Rotoiti visited Christmas Island following the test where rainout into the lagoon and concentration in the food chain may have occurred.

HARDTACK I

Watanabe et al. (1995) undertook a study to determine if Navy veterans who participated in Operation Hardtack I (1958) were at increased risk of death from certain cancers. The operation included 25 Pacific nuclear detonations mainly at Enewetak and Bikini Atolls and 2 detonations above Johnston Island.

Using the Defence Nuclear Agency (DNA) data base, 13,910 verified Hardtack series participants were identified. After the exclusion of civilian personnel, veterans who served in multiple tests series, and military personnel from branches other than the Navy, the remaining 8554 Navy veterans were included in the study cohort. A group of 14,625 non-participant Navy veterans was selected from records of the Bureau of Naval Personnel and verified as non-participants in any nuclear tests from the Nuclear Test Personnel Review (NTPR) file. Radiation dosage information was derived from individual film badges for 88% of the veterans and estimated doses were calculated for the remaining unbadged individuals by using the film badge levels of those who served in the same military unit or occupation. Participants had a median gamma level of 388 mrem (3.8 millisieverts).

Summary of major findings

For the follow-up period, 1083 (12.7%) participants and 1695 (11.6%) non-participant deaths were recorded. All-cause mortality was significantly higher among the Hardtack participants compared to controls (RR = 1.10, 95% CI, 1.02-1.19). There was no significant difference between the groups in mortality rates from all-cancers, however, mortality from cancer of the digestive organs was significantly elevated in Hardtack participants (RR = 1.47, 1.06-2.04). Analyses failed to find a significant difference between the groups for mortality from any other site specific cancer, including leukaemia. After adjustment for military rank, mortality

from cancer of the digestive organs (RR = 1.47, 1.05-2.04) continued to be significant (Watanabe, et al., 1995).

When both groups were compared to National U.S. data, Hardtack participants had a significantly elevated risk of death from prostate cancer (PMR = 1.88, 1.05-3.10), however, the risk was no higher for participants compared to controls (Watanabe, et al., 1995).

Using proportional hazards modelling, Hardtack participants in each of three radiation gamma dose categories were compared with controls (0 - 250 mrem = low dose; 251 - 1000 mrem = medium dose; > 1000 mrem = high dose). Significant relative risks were observed for all cause, all cancers, and liver cancer in the high dose group; for pancreatic cancer in the medium dose group, and; for cancer of the digestive organs in the low dose roup. However, the number of deaths from liver cancer were small (Watanabe, et al., 1995).

The authors concluded that although most of the cancers suspected of being radiogenic were not significantly elevated among the Hardtack participants; and although reported radiation doses for the participants were generally under 500 mrem, the possibility that the veterans were at an increased risk of death from certain cancers could not be ruled out.

Methodological issues

Roff (1997) maintained that there was an "unhealthy soldier" effect for certain cancers among both the Hardtack veterans and non-participant veterans, suggesting that, compared with national data, the Hardtack veterans demonstrated an increased risk of certain cancers of 46% to 88%. She also criticised the study for the use of proportional mortality ratio (PMR) data for two radically different sample sizes. After re-analysing the data in accordance with the 58.48% sample difference factor, Roff (1997) suggested that there was an approximately

doubled risk for cancer of the digestive organs, pancreas and prostate and non-Hodgkin's lymphoma and nearly tripled risks for cancer of the liver in Hardtack participants compared to non-participants.

Indeed, Watanabe et al. (1995) noted that, based on cancer risk estimates derived from high-dose studies, the cancer risk observed in Hardtack participants was about 5 to 6 times larger than the projected magnitude of risk. They suggest three possible explanations. First, the observed excess risk among Hardtack participants may have been a spurious association due to statistical abberations, including multiple comparisons. Second, the risk estimates become very uncertain when applied to very low doses. Thirdly, the DNAs estimates of radiation exposure levels for the Hardtack participants might have been much lower than the actual levels. The accuracy of such measurements has been questioned, especially when dose levels are reconstructed without measurement from film badges. The authors argue, however, that exposure data for Hardtack participants should be considered more reliable than data for other test participants because Operation Hardtack had one of the highest proportions of participants with film dosimetry data.

Watanabe et al. (1995) also acknowledged other limitations of the study, including: the reliance on death certificates for cause-of-death data; the lack of information on potential confounders (such as smoking and drinking behaviours); the relatively young age of participants and the fact that more than 87% were still alive at the end of the follow-up period, and; the possibility that the lower death ascertainment for Hardtack participants could result in a bias toward an underestimate of overall mortality and specific cancer risk.

In the Marshall Islands during 1946 the U.S. conducted a series of atmospheric nuclear weapons tests code-named Operation Crossroads. Fifty years later the Medical Follow-up Agency (MFUA) reported the results of a study of the mortality experience of Crossroads participants (MFUA, 1996).

The primary comparison in the study was between test participants and a non-participating comparison cohort who were similar in age, rank-rating, military occupation, time frame of service, and sex. While the process of participation and control selection and subsequent verification is described fully in the report (MFUA, 1996), a number of points are worthy of note. Overall, the authors claim 93% to 99% inclusion of operation Crossroads military participants in the study data base. In an attempt to maintain clarity of cohort definition, the study excluded "post-Crossroads" participants (i.e. personnel who arrived in the designated area after the formal cut-off date of the operation, but within the 6 months from 1/9/46). While a few Crossroads participants (10%) also attended nuclear tests other than Crossroads, most of these (90.5%) were only at one other test. Finally, because the participant cohort was 91% Navy personnel, and Navy records were the most complete, primary analyses for the report are limited to the 38,662 Navy participants (MFUA, 1996).

Mortality data gathered from Department of Veterans Affairs records were validated by sample comparisons with other national sources. By the study cut-off date 31.3% of participants and 30.8% of the comparison cohort were known to have died. Cause of death information was available for 86.3% of participants and 89.3% of controls (MFUA, 1996).

Because available dosimetry data were not considered suitable for epidemiologic analysis, the study was based on exposure surrogate groups with "participation" status used as a general proxy for exposure (MFUA, 1996). In addition, exposure surrogate groups included "boarders" (those who boarded target ships after detonation vs those who did not) and "Engineering and Hull status" (those enlisted personnel who had an Engineering and Hull specialty vs those in other specialties).

The primary method of analyses in this study was the proportional hazards analysis model, formulated to take into account the varied lengths of follow-up and other time-dependent effects (MFUA, 1996). Using survival time since Operation Crossroads as the dependent variable, the model was used to estimate the risks associated with possible explanatory factors, including exposure, while mathematically adjusting for potential confounders (e.g. age, rank, paygrade). The study compared the survival times of participants and controls and examined three principal causes of mortality: all-cause, all-cancer, and leukaemia.

Summary of major findings

Results showed that Navy participants in Crossroads had significantly higher mortality than non-participating military controls (RR = 1.046, 95% CI, 1.02-1.074). Participants experienced slightly higher but non-significant mortality from all malignancies (RR= 1.014, 0.96-1.068) and from leukaemia (RR = 1.020, 0.75-1.39). While the rates for malignancies and leukaemia were lower than for many other causes of death, the increase in all-cause mortality did not appear to concentrate in any of the subcategories of mortality considered. There were no statistically significant increases found for mortality in any of the 44 specific cancers and diseases examined.

Navy mortality due to all malignancies and leukaemia did not vary substantially among exposure surrogate groups. While both boarding and non-boarding participants had significantly higher all-cause mortality than non-participating controls (RRs = 1.057 (1.014-1.10) and 1.043 (1.015-1.073), respectively), the risk to boarders was not significantly different from non-boarders. Aside from all-cause mortality, risks for boarding participants did not significantly exceed those for controls for any of the disease categories, and were similar for boarding and non-boarding participants.

Enlisted participants with an E&H occupational specialty had a slightly lower, but non-significant, all-cause mortality than participants in other occupational specialties (RR = 0.99 (0.95-1.038). While the rate ratios were somewhat higher for all malignancies and leukaemia (1.051 (0.97-1.14) and 1.51 (0.94-2.44 respectively), neither were significant. Similarly, there were no significant differences recorded in mortality risk ratios between E&H controls, non-E&H controls.

The authors noted that the earlier MFUA "Five Series" study (Robinette et al., 1985) was criticised for using SMRs as its sole risk comparison, and acknowledged that the healthy soldier effect is a significant drawback to SMR use. However calculations were made to allow for comparison with previous research findings. SMRs for all-cause mortality, all malignancies and leukaemia, respectively, were: 0.87, 0.82 and 1.0 for participants and 0.83, 0.82 and 1.1 for controls.

Conclusions

The MFUA concluded that the findings did not support the hypothesis that exposure to ionizing radiation was the cause of increased mortality among Crossroads participants. They argue that, had radiation been a significant contributor to increased risk of mortality, there

should have been significantly increased mortality due to malignancies, particularly leukaemia, in participants thought to have received higher radiation doses relative to participants with lower doses and to unexposed controls (MFUA, 1996). On the premise that personnel who boarded target ships represented a more highly exposed surrogate group, a dose-response relationship could be hypothesised with controls at no dose, non-boarding participants at some dose, and boarding participants at a higher dose. Such a dose-response relationship not observed in data (MFUA, 1996).

In an attempt to assign doses to Crossroads participants, DNA considered personnel assigned to E&H occupations as a potential high exposure group. however, analyses designed to test whether E&H personnel had higher mortality, after adjusting for paygrade & age shoed no significant elevations of mortality from all-causes, malignancies, or leukaemias in E&H participants compared with non-E&H participants. More importantly, comparisons within controls also yielded similar and non-significant results.

Methodological issues

The report identified a potential self-selection bias in the participant cohort: "participants who died of a disease (particularly cancer) may have been more likely than healthy participants to have identified themselves to the NTPR, and hence become part of this study". Such a bias could account for the finding of increased relative risk for all-cause mortality among Crossroads participants relative to a comparable military comparison group. The authors argue that this is unlikely, however, given the completeness of the participant roster and the fact that mortality from all malignancies and leukaemias, was lower, not higher, than the increase in all-cause mortality. Rather, they suggest that the elevated risk of all-cause mortality in Crossroads participants is probably the results of two factors: an unidentified factor, other

than radiation, associated with participation in, or presence at, the Crossroads test; and a self-selection bias within the participant roster (MFUA, 1996).

Concerns have been raised about the validity of the MFUA control group. Roff (1997) queried the exclusion of so-called "post-Crossroads" participants, claiming that the control group may have been contaminated by the inclusion of men who had participated in the clean-up and decontamination periods. Furthermore, it was noted that a few participants attended nuclear tests other than Crossroads, this may also be the case for some of the controls. The authors contend that while such a criticism would be valid had the study been an evaluation of low-level radiation, it was in fact concerned with the comparison between crossroads participants and non-crossroad military personnel (Johnson, 1997).

A-bomb survivor incidence studies

Since 1950, the Atomic Bomb Casualty Commission (ABCC) and its successor, The Radiation Effects Research Foundation (RERF), have studied a fixed cohort of atomic bomb survivors and comparison subjects to ascertain the effects of A-bomb radiation on mortality. Prior to 1987 published reports from the "Life Span Study" (LSS) were based on a system of dosimetry (T65D) about which there were serious concerns. After extensive reassessment of the A-bomb dosimetry, revised dose estimates were calculated for the LSS cohort on the basis of the new Dosimetry System 1986 (DS86) (Schull, 1995). The reassessed estimates revealed the average dose equivalent to each city to be smaller than previously estimated and that the neutron component of the dose no longer appeared to be of major importance in either city. As a result, lifetime risk of cancer attributable to a given dose of gamma radiation now appears somewhat larger than formerly estimated. (BEIR V, 1990).

Most ABCC/RERF reports have been concerned with cancer mortality among atomic bomb survivors, few have addressed cancer incidence. However, improvements in the Hiroshima and Nagasaki tumour registries made possible an evaluation of cancer incidence in the LSS cohort (Mabuchi, et al, 1994).

Thompson et al., (1994) presented comprehensive data on incidence of solid cancer and risk estimates in the extended LSS cohort. Solid tumours diagnosed between 1958 and 1987 were ascertained by linking the LSS cohort database to the tumour registries. Consistency of the data for both cities was achieved by reviewing all previously collected data. Depending on the cancer site, DS86 organ or kerma doses were used for computing risk estimates. Among almost 80,000 survivors, 8613 developed primary solid cancers (i.e. all malignant tumours,

excluding tumours of the blood and blood-forming organs, plus brain and central nervous system tumours of benign and uncertain behaviour) (Thompson et al., 1994).

The results showed a statistically significant excess risk for all solid cancers [excess relative risk at 1 Sv ($ERR_{1\ Sv}$) = 0.63]. Significant radiation associations were also observed for cancers of the stomach ($ERR_{1\ Sv}$ = 0.32), colon ($ERR_{1\ Sv}$ = 0.72), lung ($ERR_{1\ Sv}$ = 0.95), breast ($ERR_{1\ Sv}$ = 1.59), ovary ($ERR_{1\ Sv}$ = 0.99), urinary bladder ($ERR_{1\ Sv}$ = 1.02), thyroid ($ERR_{1\ Sv}$ = 1.15), liver ($ERR_{1\ Sv}$ = 0.49), and non-melanoma skin cancer ($ERR_{1\ Sv}$ = 1.0). There was also some indication of an association between radiation and an increase in tumours of the neural system (excluding the brain) among persons aged less than 20 at the time of bombing. There was no significant excess risk for cancers of the oesophagus, rectum, gallbladder, pancreas, larynx, uterine cervix, uterine corpus, prostate, kidney and renal pelvis. While there was no significant effect reported for cancers of the oral cavity and pharynx as a group, there was a strong association between radiation and salivary gland cancer ($ERR_{1\ Sv}$ = 1.77) (Thompson et al., 1994).

The findings in relation to salivary gland tumours were supported by subsequent reports which showed that the risk from both benign and malignant tumours, particularly the latter, increased with increasing dose (Land et al. 1996; Saku et al., 1997). Malignant tumours as a group and mucoepidermoid carcinoma in particular, and benign tumours as a group and Warthin's tumour in particular, were significantly associated with radiation dose (Land et al. 1996; Saku et al., 1997).

In the Thompson et al. (1994) study, combined solid tumour analyses showed a trend for a decreasing relative risk with increased age at exposure and a twofold greater risk for females than males. More specific analyses found females to have a higher excess relative risk of

cancers of the lung, total respiratory system and urinary system. The excess relative risk decreased with increased age at exposure for combined digestive, stomach, non-melanoma skin, breast, and thyroid cancers. For solid cancers combined, the excess cancer rate increased with increasing attained age and was roughly proportional to the background incidence rate. Unadjusted for age at exposure, the ERR for most sites tended to decrease with increasing attained age. Thompson et al. (1994) reported that for some cancers (colon, breast, central nervous system, and kidney) models that allowed the ERR to vary with attained age fit at least as well as models that included age-at-exposure effects. For all solid tumours, excess cancers increased with time since exposure, based on an absolute risk model. Averaged over all ages at exposure, the relative risk decreased with time since exposure. Examination of temporal patterns by age-at-exposure groups suggested that the excess relative risk decreased with time for the younger age-at-exposure groups and remained virtually constant for the older cohorts (Thompson et al., 1994).

Preston et al. (1994) undertook a comprehensive analysis of the incidence of leukaemia, lymphoma, and multiple myeloma in the LSS cohort. Using the Leukaemia registry and the Hiroshima and Nagasaki tumour registries, a total of 290 leukaemia, 229 lymphoma, and 73 myeloma cases were identified. Analyses focused on time-dependent models for excess absolute risk. Separate analyses were carried out for acute lymphocytic leukaemia (ALL), acute myelogenous leukaemia (AML), chronic myelocytic leukaemia (CML) and adult T-cell leukaemia (ATL). Few cases of chronic lymphocytic leukaemia were recorded. There was strong evidence of radiation-induced risks for all subtypes except ATL, and there were significant sub-type differences with respect to the effects of age at exposure and sex and in the temporal pattern of risk (Preston et al. 1994).

The AML dose-response function was non-linear, whereas there was no evidence against linearity for the other subtypes. When averaged over the follow-up period, the excess absolute risk (EAR) estimates (in cases per 10^4 PY Sv) for leukaemia subtypes were 0.6, 1.1 and 0.9 for ALL, AML and CML respectively. The corresponding estimated average $ERR_{1\,Sv}$ values were 9.1, 3.3 and 6.2 respectively. There was some evidence of an increased risk of lymphoma in males (EAR = 0.6) but no evidence of any excess in females. There was no evidence of an excess risk of multiple myeloma in the standard analyses (Preston et al. 1994).

Ron et al. (1995) examined the incidence of benign gastrointestinal tumours among the LSS cohort and identified 470 such cases. A dose-response relation was observed for stomach tumours ($ERR_{1\,Sv} = 0.53$) but there was little evidence of a dose response for colon tumours and no evidence for rectal tumours. The results for benign stomach tumours was consistent with the findings of excess stomach cancer, but the excess relative risk for benign colon cancer was less than that reported for colon cancer (Ron et al, 1995).

Using data from the Adult Health Study cohort collected during 1958-1986, Wong et al. (1993) examined the relationship between exposure to ionizing radiation and the incidence of 19 non-malignant disorders in A-bomb survivors. Significant excess risk was detected for uterine myoma, chronic liver disease and cirrhosis, and thyroid disease (presence of one or more non-cancerous thyroid conditions). The incidence of myocardial infarction was shown to be increased in later years among the younger heavily exposed subjects. Indication of involvement of radiation in development of liver diseases. An effect of age at exposure was detected for non-malignant thyroid disease, with increased risk those exposed who were under 20 years of age, but not for older survivors (Wong et al., 1993).

From a comparison of cancer incidence and mortality in atomic bomb survivors, Ron et al. (1994a) reported that, even though the data sets vary in many respects, the overall conclusion regarding which solid cancer sites demonstrate a significant dose response generally confirm mortality findings. Significant excesses were observed for all solid cancers, and for caners of the stomach, colon, lung, breast, ovary and urinary bladder when either incidence or mortality data are evaluated. A significant excess of liver cancer was found in both data sets when liver cancer was defined as primary liver cancer or liver cancer NOS on the death certificate. No significant effect of radiation was seen for cancers of the pharynx, rectum, gallbladder, pancreas, nose, larynx, uterus, prostate or kidney in either series. Different results stemming from both sets were infrequent. Excess incidence rates of non-melanoma skin cancer were not supported in mortality data, and cancers of thyroid and salivary gland showed an excess incidence but were not evaluated in the mortality studies examined (Ron et al., 1994a).

Compared with the findings for solid tumours, the results for the haematopoietic and lymphatic tumours were less consistent. Although excess risks of leukaemia were found using either incidence or mortality data, significant ERRs and EARs of multiple myeloma were seen in the mortality analysis but not in the incidence data. There was also some evidence of an increase in non-Hodgkin's lymphoma among males when incidence data were analysed but no such evidence in the mortality data.

Methodological issues

The LSS population has been described as the most important single cohort for estimating cancer risk from gamma radiation because of its large size and the wide range of doses represented (BEIR V, 1990). While such data allows for making determinations of dose-response and the effects of modifying factors on the major site cancers, it is limited by a number of factors (BEIR V, 1990).

The cohort of Japanese survivors is not representative of a normal Japanese population, apart from their radiation exposure (BEIR V, 1990). Schull (1995) describes how Hiroshima and Nagasaki were not typical of Japanese cities in a number of respects. As would be expected in a nation at war, young adult males in active military service were largely absent at the time of bombing. Further, the systematic bombing of Japan prior to the A-bomb detonations led to the evacuations of many younger children and pregnant women to the countryside. Never-the-less, children and the elderly perished, in consequence of the bombing, at a greater rate than did young adults (BEIR V, 1990). Due to the worsening economic conditions, and Japan's isolation in the world, food and medical supplies were restricted and may have impacted on survivor recovery.

As discussed previously, Roff (1995) documents the development of what she calls an "article of faith" ABCC/RERF researchers reflecting a belief that there was no residual radiation in either Hiroshima or Nagasaki. It has already been noted that the reliance on A-bomb survivor studies as "benchmark" or "classic" studies is a contentious issue, and that the extrapolation of risk estimates derived from these studies to other populations is fraught with problems and must only be made with extreme caution.

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