

The Role of Epidemiology in the Detection of Harmful Effects of Radiation

Alice Stewart

Department of Public Health and Epidemiology, University of Birmingham, Edgbaston, Birmingham, United Kingdom

Data relating to acute injuries of atomic bomb survivors show that the life span study cohort is biased in favor of exceptionally low levels of radiosensitivity. These data also show that factors influencing the death rates of this cohort include irreversible damage to the immune system. These impressions are still awaiting confirmation. Meanwhile, the Oxford Survey of Childhood Cancers and surveys of nuclear workers show that at low dose levels the cancer risk is much greater than estimates based on atomic bomb survivors; the special association between leukemia and radiation is an exclusively high dose effect, and levels of radiosensitivity are much lower in the middle of the life span than at either extreme. *Key words:* competing causes of death, immune system dysfunction, late effects of radiation. *Environ Health Perspect* 108:93–96 (2000). [Online 21 December 1999]

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There is widespread agreement among nuclear scientists that the best method for estimating cancer effects of ionizing radiation is linear extrapolation of the high dose effects observed in atomic bomb survivors, and that the risk is much greater for leukemia than for other neoplasms. As a result of this consensus, the cancer risk coefficients in the Biological Effects of Ionizing Radiation (BEIR) V (1) and the International Commission on Radiological Protection (ICRP) 60 (2) are based on atomic bomb data. These documents are also based on methods of risk analysis which assume that there is no interference from cell death effects of radiation even in cases where a high dose exposure was followed by a short-lived leukocytosis and prolonged loss of immunologic competence (3) (Figure 1).

In a lengthy follow-up of atomic bomb survivors, there is no mention of these exclusively high dose effects (4). However, the leukocytosis could easily have left the marrow component of the reticuloendothelial system (RES) with an exceptionally large number of mutant stem cells. Therefore, there is a clear need to compare atomic bomb data with data from exclusively low dose situations. Two sets of atomic bomb data are especially suitable for this purpose. The first describes the cohort that was assembled from census data 5 years after the bombing of Nagasaki and Hiroshima in 1945 [life span study (LSS cohort)], and the second describes the subjects in several studies of teratogenic and carcinogenic effects of fetal irradiation (*in utero* cohort) (4). Two other data sets are also useful: one describes the first survey to find evidence of a cancer risk at low dose levels [the Oxford Survey of Childhood Cancers (OSCC) data] (5) and the other describes the first survey of nuclear workers to find evidence of a cancer risk at supposedly safe dose levels (Hanford [Washington] data) (6).

LSS Cohort

The official ICRP position regarding the late effects of the atomic bomb radiation is largely the result of continuous mortality surveillance of the LSS cohort and repeatedly arriving at the same conclusions. First, there are no late effects of the radiation apart from cancer; second, there is no cancer risk at the dose levels likely to be encountered by nuclear workers; third, there is a greater risk of leukemia than of solid tumors (with relatively short intervals between exposure and death for the leukemia cases); and fourth, there are higher levels of radiosensitivity toward the beginning rather than the end of adult life (4).

On the strength of these findings it is widely assumed that atomic bomb survivors, apart from their radiation dose, are representative human beings and, consequently, that the levels of radiosensitivity are the same not only for survivors and nonsurvivors, but also for survivors with and without acute injuries. For example, in BEIR V (1), where cancer risk coefficients are based on 75,991 members of the LSS cohort, there is no mention of the fact that RES damage evoked different reactions from lymph node and red marrow (Figure 1), or the fact that a few survivors from a massive epidemic of acute RES damage were still showing signs of faulty leukopoiesis as late as 1956 (7).

After census identification of persons who were still alive on 1 October 1950, exposure positions, shielding, flash burns and three types of cell death effects, namely oropharyngeal lesions, purpura, and epilation were systematically recorded (8). The exposure positions and shielding information were needed for dose estimation, and epilation claimants were included both in laboratory studies of RES damage (4) and in a statistical analysis which showed that for 1,308 claimants the dose–response curve for

leukemia was exceptionally steep (9). However, as a result of the Jablon et al. (10) 1965 decision that inaccurate recording of acute injuries had rendered the acute injury data useless (10), there was no further mention of the burns or the cell death effects in a series of mortality reports by the Radiation Effects Research Foundation (RERF; Hiroshima and Nagasaki, Japan) and its former organization, the Atomic Bomb Casualty Commission (ABCC).

For several decades after the 1945 bombing of Japan, the only distinctive effect of RES damage (aplastic anemia) remained a relatively common and dose-related cause of death (11). However, the LSS death rate for diseases of blood and blood-forming tissues was higher than normal; Beebe et al. (12) regarded this as part of the special relationship between leukemia and radiation. They also ignored a suggestion by Stewart (13) that the normal noncancer death rate of the LSS cohort might be an artifact. According to the Stewart (13) hypothesis, the extra deaths before 1950 left the LSS cohort biased in favor of exceptionally healthy persons, although it was not obvious because deaths from incomplete repair of RES damage continued long after 1950. By regarding this as an untestable hypothesis—but nevertheless allowing the general release of a limited amount of LSS data in the form of *LSS Data on Disk* (14)—the RERF made it possible for Stewart and Kneale (15,16) to discover that for all causes of death except cancer and cardiovascular diseases, the LSS death rate was negatively correlated with dose below the threshold for excessive marrow damage and positively correlated with dose above this level (Figure 2) (15). Among the survivors whose doses exceeded 1 Gy, there were few persons who were younger than 10 years of age or over 50 years of age when exposed (Figure 3) (16).

These observations made it appropriate to take a closer look at the injury data. The RERF added to *LSS Data on Disk* (14) the records needed to distinguish between 2,601 survivors who claimed at least two acute injuries; 63,072 survivors who denied all four injuries; and a residual group consisting

Address correspondence to A. Stewart, Department of Public Health and Epidemiology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. Telephone: 44 121 414 7497. Fax: 44 121 414 7878. E-mail: a.walker@bham.ac.uk

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of 10,318 survivors who either had no injury data (1,949), an incomplete set of denials (1,686), or claimed only one injury (6,683) (Table 1). The statistical analyses that followed this classification of the 75,991 survivors in BEIR V are still awaiting publication in a peer-reviewed journal. However, there are tables and figures included in

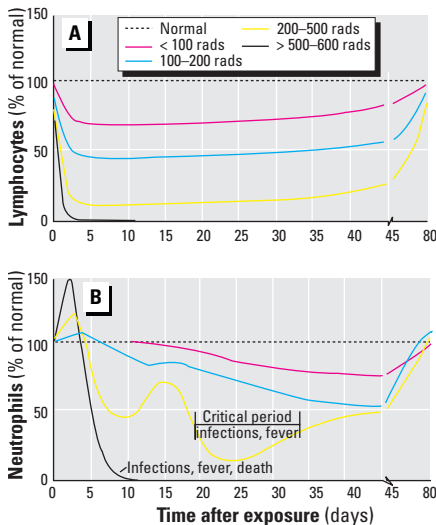


Figure 1. The changes with time after exposure to various doses of ionizing radiation in two hematologic parameters—lymphocytes and neutrophils. Data from Schull (4).

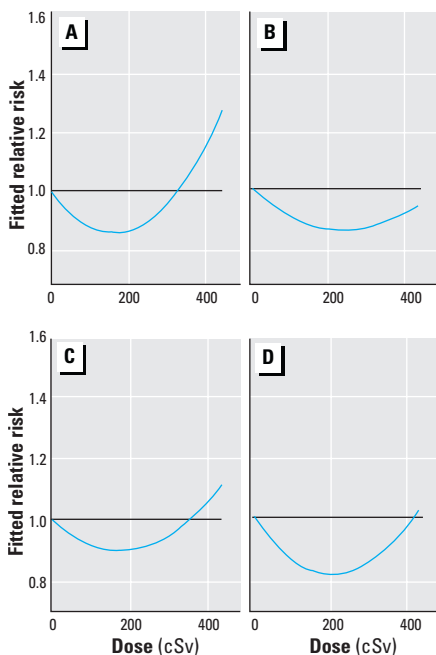


Figure 2. Fitted relative risk for all causes of deaths except cardiovascular disease and cancer: deaths between 1950 and 1982 of atomic bomb survivors in four exposure age groups. (A) age 0–19, 1,547 deaths; (B) age 20–34 years, 1,230 deaths; (C) age 35–49 years, 3,705 deaths; (D) age \geq 50 years, 6,052 deaths. Data from Stewart and Kneale (15).

Stewart and Kneale (17) that support the following conclusions: for the cohort as a whole and for the survivors who denied all four injuries, there was no evidence of any late effects of the radiation apart from cancer; in addition, levels of radiosensitivity were higher before 30 years of age than after. In the small group of survivors who claimed multiple injuries, cancer was not the only cause of extra (dose-related) deaths, and levels of radiosensitivity were higher for the youngest and oldest of six exposure ages than for any of the intervening age groups (Figure 4). Stewart and Kneale (17) also included tests of cohort homogeneity which showed that for several causes of death (including cancer), there were significant differences between the survivors who claimed multiple injuries and the other survivors. They also included figures which showed that it was only in the small group of survivors who claimed multiple injuries that the proportion of leukemias among the cancer deaths was higher than normal (Table 1).

OSCC Data

The survey that first found evidence of a cancer risk at low dose levels did so by comparing each dead child in a nationwide sample of early cancer deaths with a live child from the same regional birth cohort (5). When these comparisons showed that the dead children had been more often X-rayed before birth than the live children, new targets were set, and the Oxford survey (5) gradually became an important source of information under various headings including cancer effects of fetal irradiation and the etiology of childhood cancers (18).

The new targets necessitated a long-period of data collection that eventually produced both interview data for a long series of case-control pairs (with supplementary data from family doctors, antenatal clinics, and X-ray departments) and regional data for each 10-km square of the national grid (19). The latter included annual numbers of live births, stillbirths, and infant deaths (1943–1974); independent measurements of background radiation doses (supplied by the National Radiological Protection Board, Aldermaston, England); annual numbers of cancer deaths of children younger than 16 years of age (1953–1979); and interview data for most of these cases and their matched controls (who were now representing all members of the regional birth cohorts with cancer cases).

Several conclusions have been made from numerous comparisons between the OSCC cases and their matched controls. First, the usual time to perform X rays on pregnant women (the third trimester) is later than the usual time to initiate a childhood

cancer (the first trimester) and, after these early low-dose exposures, the risk is no greater for leukemia than for other neoplasms (20,21). Second, the cancer risk is much greater for first- as compared to third-trimester exposures (22); even during the less dangerous period, however, a dose of 10 mSv might be sufficient to double the normal risk of an early cancer death (20). Third, in addition to the X-ray data, there is also evidence that during the latent phase of all childhood cancers (especially leukemia) there is mounting sensitivity to infections (23), and evidence that in countries with high rates of infant mortality this effect of the cancer process is the cause of a strong negative correlation between early deaths (0–4 years of age) ascribed to leukemia and pneumonia (24).

Study evidence from comparisons between different parts of Britain shows that childhood cancers have a naturally clustered distribution, with higher death rates in rural areas than in large cities; the causes of childhood cancers include *in utero* exposure to background radiation as well as prenatal X rays; and factors that affect the number of early cancer deaths include both pregnancy illnesses and postnatal infections (19). There is still no explanation why the worldwide increase in childhood leukemias that followed the discovery of sulphonamides (and had nothing to do with obstetric radiography) was solely the result of lymphatic cases (25). It is possible that this unique feature of childhood leukemias is the result of myeloid and lymphatic leukemias with fetal origins that do not have the same competing causes of death (18,26).

According to this hypothesis, mutations during embryogenesis have teratogenic as well as carcinogenic effects. However, although mutations in lymphatic components of the RES cause faulty maturation of immunoglobulins and lymphatic leukemia, mutations in myeloid components cause faulty maturation of hemoglobin and myeloid leukemia. Infections are competing causes of death for both types of leukemia, but in myeloid leukemia cases, intolerance of low oxygen pressures (from faulty erythropoiesis) may lead either to a stillbirth during the second stage of labor or to a sudden death during the shallow breathing of deep sleep. Several observations support these theories. In children with myeloid leukemia and in cases of the sudden infant death syndrome, there are exceptionally high levels of fetal hemoglobin and other signs of faulty erythropoiesis (27,28). In children with Down syndrome and other congenital diseases where there is faulty maturation of the immune system, there is an exceptionally high risk of dying from lymphatic leukemia that only became obvious after antibiotics were

discovered (18). In addition, childhood cancers are only common in tissues that are not essential for *in utero* survival, e.g., the brain.

The Oxford survey (5) provided evidence that after exposure to a small dose of radiation the cancer risk is the same for leukemia and solid tumors. The survey also provided evidence that childhood cancers are the result of mutations which have teratogenic as well as carcinogenic effects, and that infections are competing causes of death for cancers of the immune system, including leukemia, lymphoma, and myeloma. As a result of these associations, only populations with low rates of mortality show common incidences of leukemia, and the relationship between age and cancer mortality has been the same for leukemia and other neoplasms only since the discovery of antibiotics (29).

In Utero Cohort

Studies of 1,500 persons who survived *in utero* exposures to atomic bomb radiation provided several impressions: there were no teratogenic effects of the radiation apart from microcephaly; there was no risk of microcephaly after exposures before 8 weeks of fetal age (4); there was no equivalent of the OSCC findings for prenatal X rays (1); and there were no childhood leukemia cases among 14 cancers that presented before 40 years of age and there were only four male cases (30). For the *in utero* cohort there is no equivalent of *LSS Data on Disk* (14). From various publications, however, it is possible to deduce that there is gross underrepresentation of exposures in the *in utero* cohort before 8 weeks of fetal age (16). This deficit is probably the result of the young embryo's exceptional sensitivity to the lethal effects of radiation, which leaves the survivors of the abortions so caused even more strongly biased in favor of exceptionally low levels of radiosensitivity than those in the LSS cohort. Evidence of this bias includes the low sex ratio for the 14 cancer cases (males are more abortion prone than females) and the total absence of any childhood leukemias (deaths from the devastating effects of the blast probably killed all of the preleukemic children). Finally, although there was a long period when the findings for atomic bomb survivors were regarded as a reason to doubt the validity of OSCC data, it is now generally recognized that the OSCC data are a reliable source of information about the cancer effects of fetal irradiation (31). The position on occupational exposures to radiation is less certain (32), although even here there is a strong impression of a cancer risk at dose levels that showed no signs of a cancer risk in atomic bomb data.

Hanford Data

The use of a maximum permissible dose and compulsory requirements for nuclear workers to wear radiation badges have ensured that the U.S. nuclear establishment is reasonably certain that routine work in nuclear facilities will not be a cause of occupationally induced cancers (6). This assumption was originally based on atomic bomb data and was also supported by Gilbert and Marks (32), who discovered that the total number of cancer deaths of Hanford workers was small by national standards; they found no evidence of any extra dose-related cancers. Meanwhile, the original survey of Hanford workers by Mancuso et al. (33) conveyed some very different impressions.

According to Mancuso et al. (33), the relatively low cancer death rate was the result of selective recruitment of exceptionally healthy persons into the nuclear industry. However, Kneale and Stewart (34), the second report, included an analysis which showed that, provided each annual dose of each worker is allowed, there is a separate contribution to the total risk. Therefore, it is possible to detect a cancer risk at dose levels only a fraction higher than background radiation, and it is possible to show that this is largely the result of exposures after 50 years of age. Furthermore, as with OSCC data (5), the extra cancer deaths of Hanford workers in the Kneale et al. (34) study showed no signs of any special association between leukemia and radiation.

In 1996, a World Health Organization survey (35), which allowed pooling of data from seven cohorts of nuclear workers in three countries, found no evidence of a cancer risk at low dose levels and consequently concluded that atomic bomb data are a reliable source of cancer risk coefficients (35). Meanwhile, the inclusion of workers from two of the seven cohorts (Hanford and Oak Ridge, TN) by Kneale and Stewart (34) revealed significantly different standards of dose estimation in the two facilities. Independent studies of Oak Ridge and Rocketdyne (Santa Susana, CA) workers also found evidence of a cancer risk at supposedly safe dose levels and discovered that this was largely the result of exposures after 50 years of age (36,37).

Conclusions

There are now three analyses of LSS data with findings that are difficult to reconcile with common assumptions about atomic bomb survivors and the late effects of radiation. These analyses include a 1991 analysis by Neriishi et al. (9), which showed that the dose-response curve for leukemia was exceptionally steep for 1,308 survivors whose injury claims included epilation; a 1992 analysis by Shimizu et al. (38), which found

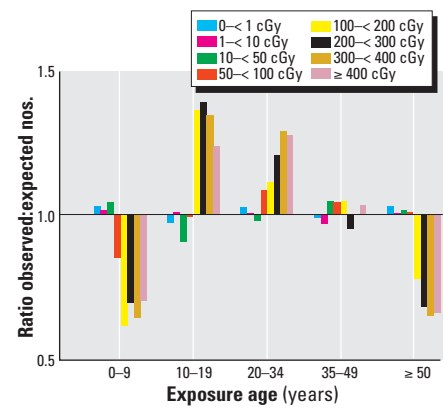


Figure 3. Ratio of observed to expected numbers for five sets of LSS data classified by exposure age and the standard estimate of dose made in 1965. Data from Stewart and Kneale (15).

Table 1. Injury data and cancer deaths for 75,991 members of the LSS cohort of atomic bomb survivors.

Claims	No.	Cancer deaths (leukemias)
Burns	5,551	—
Purpura	3,613	—
Oropharyngeal lesions	2,443	—
Epilation	1,308	—
≥ 2 injuries claimed	2,601	349 (41)
All four injuries denied	63,072	4,832 (121)
Residue ^a	10,318	755 (40)
Total LSS cohort ^b	75,991	5,936 (202)

Data from Stewart and Kneale (17).

^aIncluding 6,683 survivors who claimed only one injury, 1,949 who had no injury data, and 1,686 who had an incomplete set of denials. ^bData from BEIR V (7).

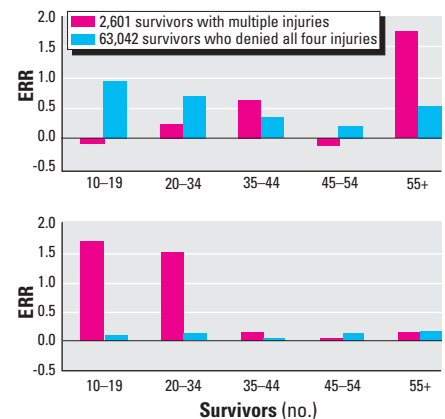


Figure 4. Excess mortality risk per Gray, atomic bomb survivors by injuries [(A) neoplasms and (B) cardiovascular diseases] and exposure age. Data from Stewart and Kneale (17). This figure does not include 186 deaths before 10 years of age. For the smaller group (with 4 deaths from malignant tumors and 2 from cardiovascular disease), the corresponding excess relative risks (ERRs) were > 7,400. For the larger group (with 91 deaths from malignant tumors and 89 cardiovascular diseases), ERRs were 1.27 and 0.30, respectively.

an excess of noncancer deaths among survivors with high doses; and the 1998 analysis by Stewart and Kneale (17). According to these analyses, the LSS cohort is not a homogeneous population, and this heterogeneity is probably the result of high doses that cause irreversible damage to the RES and that have immune system effects which were felt by survivors as well as nonsurvivors.

There are a few studies of nuclear workers that failed to find any evidence of a cancer risk at low dose levels (32,35). However, there are increasing numbers of studies whose findings are indicative of a cancer risk at supposedly safe dose levels. According to these surveys the risk at low dose levels is no greater for leukemia than for other neoplasms, and because it increases progressively with age, exposures after 50 years of age are especially dangerous (34,36,37). Together with OSCC data for *in utero* exposures, these findings are compatible with much higher levels of radiosensitivity at the beginning and end of the life span than during the intervening years (Figure 5). Because this is also true of sensitivity to infections, we can be reasonably certain that there is strong immune system control of mutant cells as well as by foreign organisms.

Other findings of the OSCC (5) and the *in utero* cohort of atomic bomb survivors include evidence of early loss of immunologic competence in all childhood cancers, especially leukemia, and strong competition between teratogenic and carcinogenic effects of early mutations. Therefore, factors that influence the frequency of childhood cancers include not only infections (and antibiotics) but also

faulty maturation of tissues which are essential for *in utero* and neonatal survival.

Various sources of epidemiologic data have provided findings which make it reasonable to assume that the LSS cohort is not only biased in favor of exceptionally low levels of radiosensitivity but also includes examples of persons who have sustained irreversible damage to the immune system. As a result of these biases, atomic bomb data are not a reliable source of cancer risk coefficients, but they can still be used to study factors with immune system associations.

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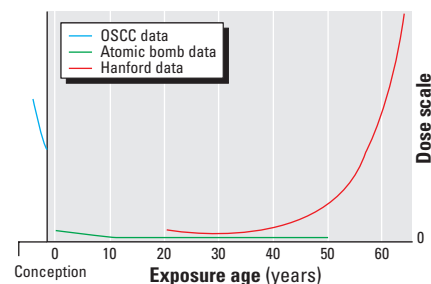


Figure 5. Relationship between exposure age and cancer risk in the study populations. Data from Stewart (39).