RERF update RERF

News & Views from the US–Japan Radiation Effects Research Foundation
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IAEA's International Chernobyl Project Outcome Corroborates Earlier Findings

In late May, the International Chernobyl Project announced its general corroboration of earlier local findings regarding the environmental and health situation in areas of the Soviet Union affected by the Chernobyl accident. Concentrating on health assessments of residents from contaminated areas—some of whom were evacuated from the now prohibited zone around the reactor site—the project was not able to address health issues relevant to all evacuees or thousands of emergency personnel brought into the region temporarily for accident management and recovery work.

"The assigned task was a formidable one," remarked RERF Chairman **Itsuzo Shigematsu**, who served as chairman of the project's International Advisory Committee. "As a result of unavoidable constraints on time, manpower and funds, the project focused on questions of continuing mass relocation of people, and sought to provide sound scientific bases for decisions yet to be made."

The year-long independent, multifaceted study was started in March 1990 under the auspices of the International Atomic Energy Agency (IAEA) with expert counsel drawn from various organizations of the United Nations system and the Commission of the European Communities. Several RERF staff members participated in the project: RERF Vice Chairman **J.W. Thiessen**, **Kiyohiko Mabuchi**, **Hideo Sasaki**, **Shizuyo Kusumi**, and **Naokata Yokoyama**. The latter three spent two weeks in the Ukraine conducting medical examinations of residents last fall (see *RERF Update* 2(4):6, 1990).

"The project teams applied their collective expertise and experience to sorting facts from misconceptions and radiation effects from effects not related to radiation exposure," continued Shigematsu. "By providing an understandable report, we hope to assist responsible authorities in deciding how to proceed. Only time will tell whether this has been achieved."

A. SALMGEN

The scene shortly after the explosion that ripped open Reactor No. 4 of the Chernobyl nuclear power plant on 26 April 1986.

General conclusions of the International Chernobyl Project

Due to the unprecedented nature and scale of the Chernobyl accident, early actions taken by authorities were improvised, and thus their complexity rendered a thorough investigation by the project team nearly impossible. Whenever these actions could be assessed, however, the project team found that the general response of the authorities had been broadly reasonable and consistent with internationally established guidelines prevailing at the time of the accident. Although some measures could have been better or more timely, the project report recommended that they be viewed in the context of the overall response.

To quote the report directly, "The protective measures taken or planned for the longer term, albeit well-intentioned, generally exceed what would have been strictly necessary from a radiological protection viewpoint. The relocation and foodstuff restrictions should have been less extensive. These measures are not justified on radiological protection grounds; however, any relaxation of the current policy would almost certainly be counterproductive in view of the present high levels of stress and anxiety amongst inhabitants of the contaminated areas of concern and people's present expectations. It is recognized, however, that there are many social and political factors to be taken into consideration, and the final decision must rest with the responsible authorities. At any rate, no modification introduced should lead to more restrictive criteria."

Population exposure

Found to be scientifically sound, official procedures for esti-

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New Answers to Old Questions?

by J.W. Thiessen
RERF Vice Chairman & Update Editor-in-Chief

From the beginning of the ABCC research activities, questions have been raised concerning the possibility of "accelerated aging," life-shortening, and other potential radiation effects not directly related to the induction of malignancies. A hypothesis of accelerated aging arose out of experimental work in the '30s and '40s, with rather extensive work in the '50s, but with little more than partial or suggestive support from data on man. In the late 1950s, Hollingsworth started the search for a series of physiologic parameters that might be useful for the creation of an "index of aging" to be used in studies on A-bomb survivors (*Yale J Biol Med* 38: 11–26, 1965; see also the excellent overview of aging research during the first 30 years by S. Finch and G. Beebe in *J Radiat Res* [Japan] Suppl:108–21, 1975). Before long, however, rather than concentrating on comprehensive effects such as aging, efforts were directed to major components of the aging process, particularly those related to diseases of the cardiovascular system, in which suggestions of a radiation-related effect had been found to be present at an early stage.

One of the earliest reports came out of the Adult Health Study, that of K. Yano and S. Ueda on cardiovascular disease in relation to exposure to ionizing radiation, which was based on a comparison of proximal and distal survivors in Hiroshima (ABCC TR 22-62). This report mentioned suggestive differences in the prevalence of coronary heart disease in females and of high blood pressure in both sexes. At the same time, they expressed doubts about the direct relationship with radiation, mentioning the possibility of other environmental factors and diagnostic inaccuracies. It is interesting to note that the evidence of increased cardiovascular disease in heavily exposed females has become more and more solid with the years, whereas there is no evidence anymore for differences in blood pressure as an effect of ionizing radiation. Doubts with respect to the

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Chernobyl Project

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mating doses were intended to provide results that would not *underestimate* the doses. During independent measurements of external exposure conducted under the auspices of the IAEA, 8,000 film badge dosimeters were distributed to residents of seven settlements. Ninety percent of the results were below the detection limit of 0.2 mSv for a two-month exposure period, which is in good agreement with calculational models. Whole-body counting for cesium was also carried out in nine settlements on 9,000 persons. Generally, the body content of cesium was lower than would be predicted on the basis of most models of environmental transfer, dietary intake, and metabolism. Similar results for cesium have been reported in other countries.

According to official reports, the mean absorbed thyroid dose for children from birth to seven years of age ranged from less than 0.2 Gy up to 3.2 Gy for seven surveyed contaminated settlements. Since the iodine had completely decayed by the time of the project, no independent verification of the reported absorbed doses was possible.

Independent dose estimates were made for surveyed contaminated settlements on the basis of average deposition. Estimates of 70-year (1986–2056) doses were 60–130 mSv (external), and 20–30 mSv (internal, cesium). Overall, project dose estimates for the surveyed contaminated settlements were lower than the officially reported estimates, but there is agreement within a factor of 2–3 between the two sets of estimates.

Immediate and delayed health impacts

Although significant non-radiation-related health disorders were observed in the populations of both contaminated and control settlements, project teams identified no health disorders that could be attributed directly to radiation exposure. Undoubtedly, the accident had substantial negative psychological consequences in terms of anxiety and stress due to the continuing and high levels of uncertainty, which also affected populations residing outside the contaminated areas. Socioeconomic and political changes in the USSR have served to compound these anxieties.

Project teams found that local clinical investigations of health effects had been done poorly, producing confusing, often contradictory results. The reasons for these failures included: lack of well-maintained equipment and supplies; poor information through lack of documentation and lack of access to scientific literature; and shortages of well-trained specialists. Despite these obstacles, a few competent local clinical studies were corroborated.

The vast majority of adults examined in contaminated and control settlements either believed or suspected that they had an illness due to radiation exposure. Although children were generally found to be healthy, 10–15 percent of adults (excluding those who were hypertensive) required medical care.

Available data did not provide an adequate basis for determining whether leukemia or thyroid cancers have increased as a result of the accident. But, the data lacked enough detail to exclude the possibility of an increase in the incidence of some tumor types. Reported estimates of absorbed thyroid dose in children are such that there may be a statistically detectable increase in the incidence of thyroid tumors in the future.

Population relocation

According to the project report, criteria for relocation were not wholly consistent with the principles currently recommended internationally.

One of the more important misunderstandings or misrepresentations had been confusion over, and lack of recognition of, the very different origins and purposes of the dose limits recommended internationally for controlling planned increases in radiation exposure and those of the dose levels at which intervention is prompted to reduce existing radiation exposures. Dose limits per se are not the appropriate levels at which to intervene following an accident. The dose averted by relocation should be the relevant quantity for judging the radiological benefits of relocation and, where practicable, quantitative criteria should be expressed in terms of this quantity.

According to the project report, it was not evident that considerations of averted dose were at the origin of the criteria proposed by the authorities.

Of the adults in the surveyed contaminated areas, 75 percent wanted to relocate. ❑

Noncancer Mortality in the Life Span Study, 1950–85

Among Life Span Study deaths for the period 1950–85, the authors find evidence of an excess risk of noncancer mortality in the high dose range.

by Yukiko Shimizu, Hiroo Kato,[1] William J. Schull,[2] and David G. Hoel,[3] RERF Department of Epidemiology, Hiroshima

Since 1950, the Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF), have studied a fixed cohort of A-bomb survivors and suitable comparison subjects, the so-called Life Span Study (LSS) sample, to ascertain the effects of A-bomb radiation on mortality. Periodic analyses of the results of this surveillance continue.

Recently, mortality in the Life Span Study sample has been determined for 1950–85, and an analysis of cancer deaths using the revised DS86 doses has been reported (Shimizu et al., RERF TR 12-87 and RERF TR 5-88). The evidence of radiation-related increases in site-specific malignancies continues to emerge. However, it has not been clear heretofore whether mortality from causes other than cancer is also increased and whether a life-shortening occurs attributable to these other causes of death. Previous analyses of noncancer mortality (see Kato et al., RERF TR 5-81 for the most recent) have failed to reveal evidence of either of these possibilities. However, it was noted that mortality from causes other than cancer appeared to be elevated in the highest T65 exposure group, ≥4 Gy. With the accumulation of seven more years of follow-up beyond the last analysis and using the new dosimetry, we find stronger evidence of an excess risk from noncancer mortality in the high dose range, i.e., 2 Gy or higher (Shimizu et al., RERF TR 2-91, in press). This evidence will be briefly presented here.

Among a total of 120,128 LSS sample subjects (exposed: 93,611; control: 26,517), DS86 dose estimates are available on a total of 75,991 individuals who are referred to as the DS86 subcohort. Among a total of 28,737 deaths occurring in the period 1950–85 in this subcohort, for 75 the cause was unknown; for 1,515, death was due to external causes; for 6,224, it was attributed to neoplasm; and 146 deaths were from blood disease. The remaining 20,777 deaths from "all diseases except neoplasm and blood disease" are considered in the present analysis (see table). The accuracy of the diagnosis of

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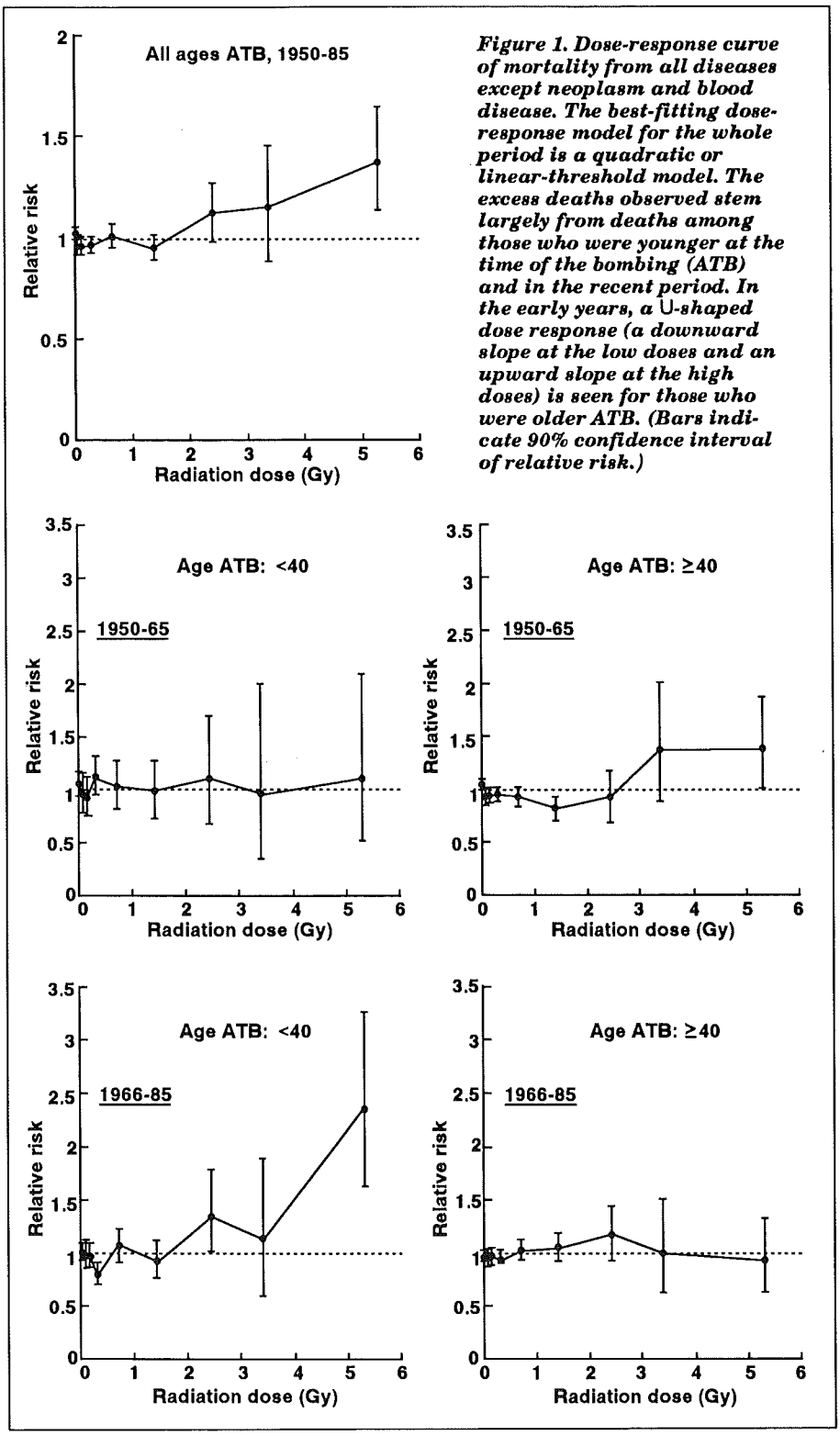

Figure 1. Dose-response curve of mortality from all diseases except neoplasm and blood disease. The best-fitting dose-response model for the whole period is a quadratic or linear-threshold model. The excess deaths observed stem largely from deaths among those who were younger at the time of the bombing (ATB) and in the recent period. In the early years, a U-shaped dose response (a downward slope at the low doses and an upward slope at the high doses) is seen for those who were older ATB. (Bars indicate 90% confidence interval of relative risk.)

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Noncancer Mortality

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death due to blood disease is very low, and such deaths often include leukemia and malignant lymphoma. Thus, we have excluded blood disease from the analysis, and the term "noncancer" will refer to all diseases except neoplasm and blood disease. The table shows the number of noncancer deaths by specific cause. About half of these deaths were ascribed to circulatory disease.

Noncancer mortality in the period 1950–85 exhibits a significant nonlinear dose response with excess risks apparent at doses of 2 or 3 Gy and over (Figure 1). Statistically, a pure quadratic or a linear-threshold model (the estimated threshold dose is 1.4 Gy and its confidence limits are 0.6–2.8 Gy) is found to fit better than a simple linear model. Generally, this increase in noncancer mortality is statistically demonstrable after 1966 and among the younger survivors ATB (<40), suggesting a sensitivity for this age group. For specific causes of death, an excess in relative risk at the high dose level, i.e., 2 Gy or more, is seen in circulatory (both stroke and heart disease) and digestive diseases (particularly liver cirrhosis) among the younger age ATB group (<40) in the recent period (1966–85). The findings on circulatory disease are supported by a cardiovascular disease (CVD) incidence study based on specific diagnostic criteria, autopsy materials, and death certificates, as well as clinical findings including ECG results.

The increased risk for noncancer mortality is much less than that for cancer. For all subjects, relative risks at 2 Gy are 1.06 for noncancer deaths (based on a linear-threshold model) and 1.78 for cancer deaths (based on a linear model). Excess deaths per 10^4 person-year-gray (PYGy) are 1.2 for noncancer and 10.0 for cancer. For those survivors less than age 40 ATB who died in the years 1966–85, the relative risks at 2 Gy are 1.19 for noncancer deaths and 2.06 for cancer deaths, and the excess deaths per 10^4 PYGy are 1.7 and 11.2, respectively.

The Gompertz function, which is the logarithm of the age-specific death rate, has been shown to describe adequately the mortality rate of most chronic diseases in the adult. The logarithm of the age-specific death rates yields a straight line, and life-shortening is suggested by an elevation of the Gompertz function. Figure 2 shows the logarithm of the age-specific death rates for noncancer in the survivors exposed to 2 Gy or more as contrasted with the comparison (0 Gy) group for those survivors exposed under age 40 ATB and for those exposed at ages ATB ≥40. In the former instance, the age-specific death rate from noncancer is elevated in the ≥2.0 Gy group as compared with that in the 0 Gy group. But for ages ATB ≥40, no elevation in the Gompertz curve is observed.

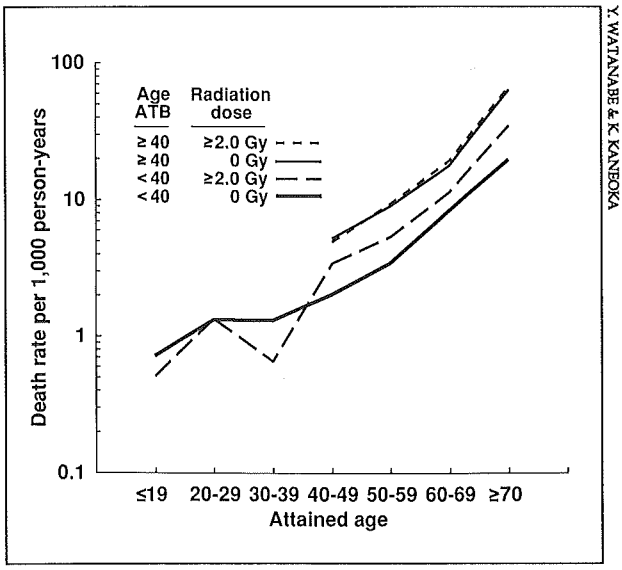


Figure 2. Age-specific death rate (per 1,000 person-years) by radiation dose and age ATB for all diseases except neoplasm and blood disease.

It is not unreasonable to assume that the effects of radiation on cancer induction (presumably stochastic phenomena) and on noncancer mortality differ, and that the latter may follow a nonstochastic process with a threshold dose. However, given the recent evidence of a transforming gene in the atheromatous plaque, the increase in CVD is a particularly intriguing finding and may suggest, if the association is real, that the effect of ionizing radiation on atherosclerosis should be treated as a stochastic phenomenon. Further data will be especially interesting in this regard.

The findings presented here, based as they are on death certificates, have their limitations. Most significant perhaps is the possible erroneous attribution of radiation-related cancer deaths to other causes. To examine the impact of such errors on the observed increased relative risk of noncancer mortality, we have used the information on classification errors revealed by the autopsy and tumor registry data that are available as well as the clinical data provided by the Adult Health Study. At present, the contribution such errors may make to the apparent increase in noncancer deaths at the higher doses cannot be estimated as rigorously as is obviously desirable. However, even now, this increase does not appear to be fully explicable in terms of classificatory errors. A formal statistical analysis of the effects of misclassification, using autopsy data, also leads to the conclusion that the observed significant dose response in noncancer mortality cannot be easily explained by misclassification of cancer (Sposto et al., RERF TR 4-91, in press; see also page 5 of this issue of *Update*).

Some evidence is found to support the selection effect hypothesized by A. Stewart and G. Kneale (*Health Phys* 58: 729–35, 1990). However, this evidence is limited to only the older ages ATB in the initial years of study. A U-shaped dose response (a downward slope in the low doses and an upward slope in the high doses) is seen for noncancer mortality among survivors whose age ATB was 40 or older and who died in 1950–65 (Figure 1). Since radiation-induced cancers (except leukemia) are observed primarily in the later period, the selection cannot affect the cancer risk appreciably.

Further follow-up of mortality in this LSS cohort, as well as disease revealed by the biennial physical examinations of the morbidity subsample (the Adult Health Study), will be needed to confirm this suggestion of a radiation-related increase in mortality from causes other than cancer and to determine whether it results in a demonstrable life-shortening among the heavily exposed A-bomb survivors. ❑

Number of deaths by cause of death among the 75,991-person DS86 subcohort, 1950–85.

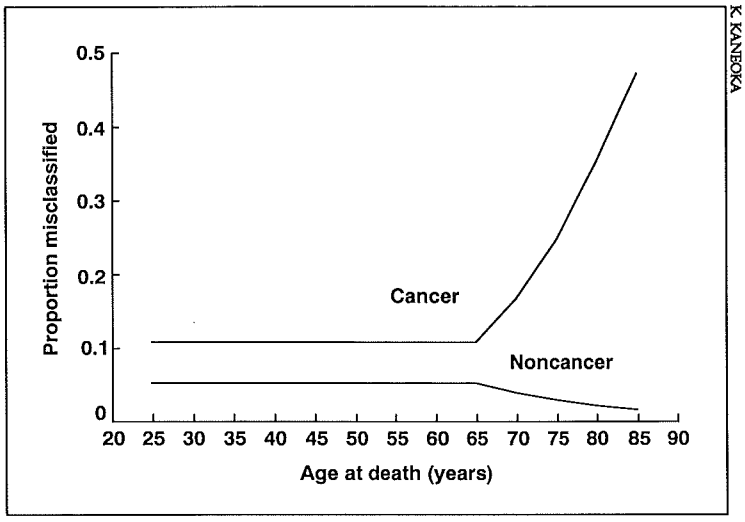
Cause of death	No. of deaths
All causes	28,737
External (i.e., accidents, etc.)	1 515
Unknown	75
All diseases	27,147
Neoplasm	6 224
Blood disease	146
All diseases except neoplasm and blood disease:	20,777
• Infectious disease	1 413
• Circulatory disease	11,164
Stroke	6 202
Heart (circulatory disease except stroke)	4 962
• Respiratory disease	2 036
• Digestive disease	2 149
• Others	4 015

Diagnostic Misclassification and Mortality in the RERF Life Span Study

Is the dose response in noncancer mortality due to misclassified cancer deaths?

by Richard Sposto,[1] Dale L. Preston,[1] Yukiko Shimizu,[2] and Kiyohiko Mabuchi,[2,3] Radiation Effects Research Foundation, Hiroshima

A primary use of the RERF Life Span Study (LSS) cohort is in assessing the effect of radiation exposure on mortality. Analyses of mortality in this cohort reveal increased risk of death from many types of cancer among radiation-exposed individuals (Shimizu et al., *Radiat Res* 121:120–41, 1990). One also observes a significant dose response for mortality from causes other than cancer, with the dose effect appearing primarily at high doses (Shimizu et al., RERF TR 2-91, in press). It has been suggested, however, that the observed dose response in noncancer mortality may result from the misclassification of cancer deaths as noncancer deaths on death certificates, which are the basis for assigning cause of death in the LSS. This question is important because if the observed noncancer dose response is due to misclassified cancer deaths, then cancer mortality risk estimates obtained from current analyses may be underestimates. An equally important issue, however, is whether the RERF data on noncancer mortality are consistent with other epidemiologic and laboratory data suggesting that the primary effect of radiation on human mortality is through increased risk of cancer. To investigate this question, we performed analyses of cancer and noncancer mortality in the LSS in which the numbers of cancer and noncancer deaths were adjusted to compensate for misclassification.



Cancer misclassification rate (θ_{CN}) ***and noncancer misclassification rate*** (θ_{NC}) ***as a function of age at death.***

The method used to adjust for misclassification is a formalization of a simple idea. Let D_C and D_N represent the numbers of true cancer and noncancer deaths, and d_C and d_N the numbers of cancer and noncancer deaths observed from death certificate data, some of which have been misclassified. (In this article, "cancer" refers to all neoplasms including leukemias and benign tumors, and "noncancer" to all nonneoplastic disease, which excludes external causes of death, such as accidents). Let θ_{CN} and θ_{NC} be the proportions of true cancers misclassified as noncancer on the death certificate, and noncancers misclassified as cancer, respectively. Then the formulas

$$d_C = D_C(1 - \theta_{CN}) + D_N\,\theta_{NC}$$

and

$$d_N = D_C\theta_{CN} + D_N(1 - \theta_{NC})$$

describe the relationship between d_C, d_N, D_C, and D_N. For example, the first equation above states that the observed cancer deaths comprise true cancer deaths which were correctly classified and true noncancer deaths which were misclassified as cancer. The bottom equation has a similar interpretation for observed noncancers. We can observe d_C and d_N directly, so if we can obtain values for θ_{CN} and θ_{NC}, we can solve for D_C and D_N and base our analysis of cancer and noncancer mortality on these corrected quantities.

In the formalization of this method, which we will not describe here, the correction is actually based on the expected values of d_C, d_N, D_C, and D_N, which, along with θ_{CN} and θ_{NC}, depend on other variables such as age at death, calendar time, age at exposure, city, sex, and radiation dose. The formal method allows us to compute likelihood ratio tests of the parameters in the models which describe cancer and noncancer mortality.

The cohort used in these analyses comprises 86,520 members of the LSS with known follow-up for whom DS86 dosimetry has been computed. Intestinal doses were selected as a reasonable representative organ dose for the many disease types and sites considered, with neutron and gamma components of dose weighted with a constant RBE of 1. (The results are essentially independent of RBE.) Data obtained by the RERF autopsy program between January 1961 and December 1975 were used to obtain estimates of the misclassification probabilities θ_{CN} and θ_{NC}. Both cancer and noncancer misclassification rates exhibited statistically significant, rapid changes in the misclassification rate with age at death for ages over about 65 years. To capture the essential characteristics of the data, we assumed that misclassification rates were constant for age at death less than 65, but were age-dependent for age at death over 65. For cancer, the misclassification rate increased with increasing age, but for noncancer it decreased with age. Functions describing θ_{CN} and θ_{NC} are shown in the figure. The overall estimated crude misclassi-

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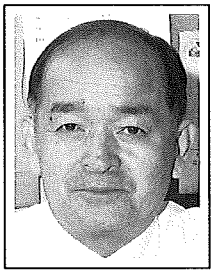
[1]*Department of Statistics,* [2]*Department of Epidemiology, and* [3]*Department of Epidemiologic Pathology.*

Noncancer Mortality Data on Disk

RERF will make available on floppy disk the Life Span Study noncancer mortality data in tabular format together with documentation. Information about availability of this data will be published in the next issue of *Update*. ❑

News Briefs

✓ Yokoro Joins RERF as Senior Consulting Scientist



Yokoro

After his retirement from Hiroshima University's Research Institute for Nuclear Medicine and Biology (RINMB) in March, **Kenjiro Yokoro** was appointed a senior consulting scientist at RERF's Nagasaki Laboratory, where he will continue to study radiation carcinogenesis. A graduate of Hiroshima Medical College, he was RINMB chief from 1981–85.

From 1958–62, Yokoro studied at three American cancer institutes and from 1964–65 at Sweden's Karolinska Institute, where he participated in experimental research on leukemia and carcinoma. In 1977, he discovered that the development of breast cancer is accelerated by giving prolactin to irradiated rats.

Yokoro is international vice chairman of the International Physicians for the Prevention of Nuclear War.

✓ In Memoriam: Donovan Thompson

Donovan Thompson, who served as RERF chief of research from October 1982–September 1983, died suddenly on 25 June in Seattle, Wash. Instrumental in recruiting numerous statisticians and epidemiologists to work at RERF in the early 1980s, Thompson was a member of RERF's Scientific Council from 1985–89.

✓ Highlights of the RERF Lecture Program

On 19 April, **Daniel Krewski**, Health and Welfare Canada, discussed additive and multiplicative relative risk in the two-stage clonal expansion model of carcinogenesis.

Robert W. Miller, US National Cancer Institute, Bethesda, Md., spoke on 1 May about the value of "bedside clues" to cancer etiology.

On 10 June, **K.F. Baverstock,** Medical Research Council, Oxon, UK, discussed DNA instability, paternal irradiation and childhood leukemia. A member of the Scientific Advisory Panel to the Marshall Islands Government, he also briefly reviewed the ongoing project to establish the radiological status of the Marshall Islands, where nuclear weapons testing occurred during the 1950s.

On 17 July, **Niel Wald**, University of Pittsburgh Graduate School of Public Health, discussed automated chromosome analysis.

✓ Research Staff News

Ohara

Hiroshima

Research Information Center: **Jill L. Ohara** was promoted to center chief on 1 June.

Department of Epidemiology: Assistant Department Chief **Suminori Akiba** is concurrently acting chief of both the Laboratory of Pathology and the Tumor & Tissue Registry Office.

Department of Radiobiology: Research Associate **Terumi Mizuno** has joined the Laboratory of Cell Biology, where she will participate in research on somatic mutations and molecular oncology. She formerly worked in the Faculty of Pharmacology, Department of Radiation Biology, Kanazawa University.

Nagasaki

Department of Clinical Studies: **Hiroaki Nonaka** is acting chief of the Division of Clinical Laboratories. **Kiyosumi Oishi** is now Nagasaki Lab's industrial health physician. **Masako Tsuruta** has joined the Division of Medicine as a research associate. Formerly employed at Showakai Hospital, she will participate in endocrinological studies. ❑

Misclassification

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fication rates were 22% for cancer and 3.5% for noncancer in this cohort.

Poisson regression methods were used to model cancer and noncancer mortality. Background rates (death rates for individuals exposed to zero dose) were stratified by city, sex, age-at-exposure category, and time category. For cancer mortality, the excess relative risk (ERR) was assumed to be a purely linear function of dose. Since preliminary analyses of total noncancer mortality showed that curvature would be an important characteristic of the noncancer dose response, the ERR for noncancer mortality was assumed to be a nonlinear function of dose.

The table summarizes the analyses of noncancer and cancer mortality without (top row) and with (bottom row) correction for misclassification. The test for the noncancer dose response is significant, with $p > 0.001$, before correcting for misclassification. After correcting for misclassification the dose response is still significant, although less so, with $p = 0.006$. This amount of misclassification does not explain the significant dose response in noncancer mortality.

Summary of the analyses of noncancer and cancer mortality without (top row) and with (bottom row) correction for misclassification.

	Test of noncancer dose response	Noncancer ERR at 1 Gy (% change)	Excess noncancer deaths (change)	Cancer ERR* at 1 Gy (% change)	Excess cancer deaths (change)
No correction for misclassification	$p < 0.001$	0.0630	129	0.848	354
Correction for misclassification	$p = 0.006$	0.0495 (–21%)	98 (–31)	0.959 (+13%)	396 (+42)

* For 50-year-old males exposed at age 25 in Hiroshima.

Given that there is misclassification of diagnosis, it is interesting also to consider what happens to estimates of common measures of radiation effect as a result of the adjustment. Notice in the table that the estimate of noncancer ERR decreases by 21% after correction for misclassification, and that 31 fewer excess noncancer deaths are predicted. On the other hand, cancer ERR increases by 13% as a result of correction for misclassification, with 42 more excess cancer deaths in the cohort. Hence one use of the methods described here is to refine estimates of radiation risk for types of cancer, such as liver cancer, which may be particularly susceptible to diagnostic misclassification.

Before accepting these results completely, it is necessary to consider how accurately misclassification rates estimated from the autopsy series reflect the amount of misclassification that has actually occurred on LSS death certificates, and how incorrectly estimating these misclassification rates can affect our conclusions. It is also necessary to refine the correction for misclassification by using more specific causes of death. Members of the Department of Epidemiology and the Department of Statistics at RERF are now performing detailed analyses of diagnostic misclassification based on the RERF autopsy series with this aim. However, it appears from our analyses so far that diagnostic misclassification is not the explanation for the observed noncancer mortality dose response. ❑

Mitigating the Effect of Inaccurate Death Certificate Diagnoses in the Life Span Study

By using broader cause-of-death categories, the diagnostic accuracy of death certificates can be improved substantially.

by Randy L. Carter,[1] Elaine Ron,[2] and Kiyohiko Mabuchi,[2] RERF Departments of [1]Statistics and [2]Epidemiology, Hiroshima

Inaccuracies in death certificate (DC) diagnoses have been noted often in the medical and epidemiological literature. The need to evaluate DC accuracy was recognized early at ABCC–RERF. By 1951, selective adult autopsy and surgical pathology programs had been initiated in both Hiroshima and Nagasaki. In 1961, a comprehensive autopsy procurement program began, focusing on the LSS cohort. Autopsy rates ranged from 30–40% in the 1960s but declined to about 10% by the late 1970s. The program was formally terminated in 1988.

Since 1961, four Pathology Study reports have been published. Most recently, T. Yamamoto et al. studied 46 cause-of-death categories among LSS cohort members for the period 1961–75 (RERF TR 18-78). Their results were similar to others' in that the accuracy of DC diagnosis was less than desirable for many categories. They observed autopsy confirmation of DC diagnosis *and* DC detection of autopsy diagnosis in greater than 70% of cases only for breast cancer, leukemia, stomach cancer, and external causes. In other words, for these causes, DC diagnoses were correct at least 70% of the time (the confirmation rate) and DCs identified more than 70% of the true cases (the detection rate).

We recently updated this study by including 60 cause-of-death categories and data through August 1987. A total of 5,130 autopsies had been performed at ABCC–RERF by this date. Confirmation rates ranged from 13–97% among specific causes that were diagnosed by DC in more than 10 cases and, overall, were greater than 70% for 15 causes. Detection rates ranged from 6–90% among specific causes that were diagnosed more than 10 times by autopsy and were greater than 70% for only 7 of the 60 categories. We observed confirmation *and* detection rates

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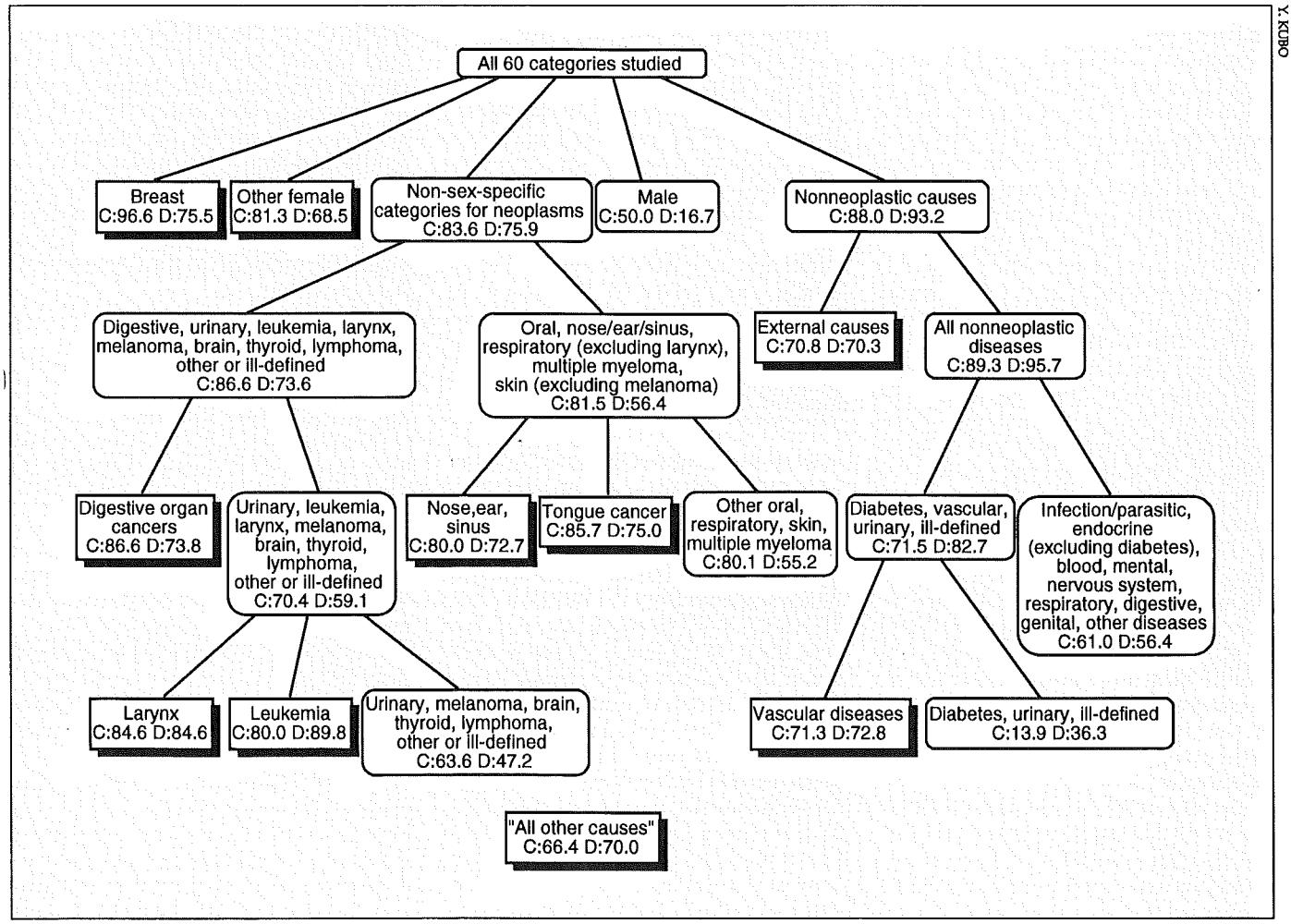

Y. KUDO

Results of the hierarchical strategy for grouping 60 ICD cause-of-death categories. Final categories are shown in the shadowed boxes.

Death Certificates

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greater than 70% for a few specific cancers only (breast, leukemia, tongue, stomach, nose/ear/sinus and larynx). Grouping by major cause of death classifications of the ICD coding system did not improve accuracy substantially. From among the 16 major categories, only "neoplasms" had confirmation *and* detection rates greater than 70%. Among the 16 major subclassifications of "neoplasm," only "digestive organs" and "breast" had both confirmation and detection rates above 70%. Death certificate inaccuracies were greater for nonneoplastic than neoplastic causes. Only cerebral vascular disease, external causes, and cirrhosis had both confirmation and detection rates greater than 40% among nonneoplastic causes studied.

These somewhat disappointing findings led us to investigate an alternative strategy for grouping causes of death into a diagnostic classification system. The strategy is summarized as follows.

First, all sex-specific cancers were excluded from the 60 initial causes of death under study. The set of remaining causes was divided into two groups in a way designed to maximize percent agreement. Confirmation and detection rates were calculated for each resulting group. Then each group having both rates greater than 70% was partitioned again. This process continued until one of the following stopping rules was satisfied: 1) if neither of the two resulting groups had confirmation *and* detection rates greater than 70%, they were recombined to form a final group; 2) if only one of the resulting groups failed the 70% criterion, it was searched for individual causes with both rates over 70%, and these were separated out to form single-cause categories, after which partitioning stopped. Final groups not meeting the 70% requirement were combined with male cancers to form an "all other causes" group. Breast cancer and other female cancers met, or nearly met, this requirement and were therefore retained as categories of the final diagnostic classification system. The results from each stage of our hierarchical grouping strategy are illustrated in the figure on the preceding page. Final categories are indicated by shadowed boxes.

By following this strategy, with minor modifications to ensure interpretability, we obtained a 10-category classification system defined by the following categories: leukemia, tongue cancer, cancer of the larynx, nasal/ear/sinus cancer, cancers of the digestive organs, female breast cancer, other female cancers, vascular diseases, external causes, and all other causes. The overall percent agreement between DC and autopsy for this statistically derived, yet biologically meaningful, classification system was 72%. Confirmation rates for the 10 classes ranged from 66% for "all other causes" to 97% for "female breast cancer." The second lowest confirmation rate was 80%. Detection rates ranged from 68% for "other female cancers" to 90% for "leukemia."

In contrast, the overall percent agreement was only 53% for a more conventional classification system, defined by major ICD classifications. Confirmation rates ranged from 18–91% and detection rates from 19–76% for the more conventional groupings.

Additionally, we considered several broader classification systems that were motivated by the results at different stages of the hierarchical clustering strategy described above. Overall agreement was very high (87–88%) when nonneoplastic diseases were grouped together and remained moderately high (72%) when vascular diseases were separated from other nonneoplasms. Any finer classification of nonneoplastic diseases, however, resulted in unacceptably low accuracy rates.

It appears that, as a group, nonneoplastic causes are diagnosed well by DC. Among more specific nonneoplastic causes, however, only external causes and vascular diseases are diagnosed adequately. This is a particularly important observation given the current interest in radiation dose effects on noncancer mortality at RERF. For example, the finding by Shimizu et al. (RERF TR 2-91, in press) of increased noncancer mortality and, more specifically, increased incidence of death from vascular diseases in heavily exposed A-bomb survivors may be regarded as more credible than their similar conclusions concerning nonneoplastic digestive disorders and specific types of vascular diseases. The question arises whether the apparent dose response for the latter two may have been due to misclassification of neoplasms or vascular diseases. Studies of specific neoplastic causes that do not possess high accuracy rates also should be interpreted cautiously.

Our results highlight a major problem to be addressed in future RERF studies on mortality due to specific causes. Investigators should be aware of the limited accuracy of DC diagnoses for most causes and even for most groups of causes. Protection against the potentially biasing effects of inaccurate DC diagnoses is obtainable by employing recently proposed statistical methods that adjust for misclassifications (see the article by R. Sposto et al. on page 5). Since the precision of such methods decreases with increasing misclassification rate, the effect of DC inaccuracies is limited further when studying causes of death among the 10 categories of the diagnostic classification system described above. In the case of neoplasms with relatively poor DC accuracy rates, mortality analyses can be accompanied, or replaced, by analyses of incidence based on the tumor registry. The AHS sample could be useful in bypassing this problem when studying specific nonneoplastic diseases not included in the above classification system. ❑

Perspectives

continued from page 2

existence of diagnostic biases, however, have continued through the years.

This issue of *RERF Update* marks the recent approval of Part 3 of Life Span Study Report 11, which concerns noncancer mortality (Y. Shimizu et al., RERF TR 2-91, in press; see page 3 of this issue of *Update*). Three articles about this subject are included here—two on the impact of misdiagnoses. LSS Report 11, Part 3 has received unusually extensive peer review, and has gone through three major revisions to incorporate responses to comments. This is appropriate, given the degree of importance inherent to what now appear to be significant, rather than suggestive, findings. Although the effect is very small (in terms of relative risk at 2 Gy, the noncancer risk is approximately 10% of the cancer risk, with a likely threshold between 1 and 2 Gy), it appears to be real, and not explainable by misdiagnoses, as a statistical study by R. Sposto et al. indicates (RERF TR 4-91, in press; see page 5 of this issue).

So, the questions may be old, the answers are not exactly new! Whether radiation exposure causes accelerated aging has become an academic issue that might more appropriately be replaced by the question of whether there is a relationship between radiation exposure and life span. The latter issue is amenable to analysis, it seems to me, given the large amount of information now in our files, and the advanced state of statistical methodology. If it is, I believe it is time that we start addressing it directly, rather than through indirect indications such as mortality and disease incidence rates, however important these may be from scientific and medical points of view. ❑

Book Review

An Environmental Odyssey: People, Pollution, and Politics in the Life of a Practical Scientist by Merril Eisenbud; University of Washington Press, Seattle, Wash., 1990; 276 pp., US $24.95.

PHOTO COURTESY OF M. EISENBUD

Eisenbud and friends atop Hijiyama in 1950.

When Merril Eisenbud started his career as a safety engineer with an insurance company a few years before the start of the Second World War, he couldn't possibly have imagined the turns and twists his life had in store for him: "odyssey" is an appropriate characterization of his autobiography. As a matter of fact, the title summarizes both the account and the accounter quite nicely. Reading his book makes those of us who have been active, in any capacity, in the "nuclear age," realize that we have been through some exciting times, and although some of that excitement may have gone (or gone sour), it is a great experience to have someone like Eisenbud bring it all to life again.

Eisenbud was an environmentalist avant la lettre, not because of a vague feeling of oneness with nature, or some such sentiment, but because of his interest as a professional in the effects of pollutants in the workplace, and later, in the environment at large. During the long period of his involvement, he was always, first and foremost, as he calls himself, a "practical scientist," not an ideological activist. His book provides the evidence that solid science, with an eye on practical applications, carries the day more often than the slogans or endless legal arguments often sold as the solution for our environmental woes.

A little more than 10 years after he started his career at Liberty Mutual, Eisenbud joined the US Atomic Energy Commission (AEC) as a member of the newly created Medical Division of the New York Operations Office (NYOO), and within two years he became the director of the division's laboratory, soon to be named the Health and Safety Laboratory (HASL). The illustrious history of this laboratory and the prestige that HASL enjoyed worldwide as a center for radiation dosimetry and environmental science are proof of Eisenbud's enthusiastic and professional leadership. It was sad that, due to the political pressures that developed in the "decade of the environment," this laboratory—once possessing a strong and clear identity—was renamed the Environmental Measurements Laboratory (EML), a trendy name that created the impression that the laboratory was not really a research institution.

During his tenure at HASL, Eisenbud became involved in both the lightest and the heaviest of the naturally occurring metals: beryllium and uranium. AEC being the largest consumer of these metals, it was Eisenbud's position that the contractors responsible for providing these products should follow safety practices and exposure standards established by NYOO, the contracting agent. Headquarters agreed with this position as far as beryllium was concerned, and the standards developed under Eisenbud's leadership were promptly adopted, not just by AEC and its contractors, but worldwide. With respect to uranium mining, however, AEC took the position that mine safety was a responsibility of the states and should not be regulated by AEC. This decision, as Eisenbud points out, was very unfortunate, and many lung cancer deaths from radon exposure might have been avoided if HASL had been allowed to provide leadership in the development of radon standards for AEC contractors. He did develop radon expertise at "his" laboratory, however, and to this day EML is among the leading research institutions in this field.

The story of a life as full as Eisenbud's cannot possibly receive adequate coverage in the framework of a book review, and I forego the temptation to elaborate on Eisenbud's involvement in the studies of radioactive fallout as AEC's NYOO manager, as a professor of industrial and environmental medicine at New York University, as New York City's first environmental protection administrator, and, finally, to this day, as an often-sought consultant in occupational and environmental health matters. I shall therefore limit my remaining remarks to his involvement with our organization.

As NYOO manager, Eisenbud was contract administrator for the Atomic Bomb Casualty Commission. At the time (1950), there was serious doubt about the viability of ABCC's research program, and Eisenbud, together with Drs. Machle (National Academy of Sciences) and Goodpasture (Vanderbilt University), was sent to Japan to investigate and recommend what should be done. On the basis of their report, AEC's Advisory Committee for Biology and Medicine did recommend that the research be terminated, but, according to Eisenbud, it was Gen. Douglas MacArthur's personal intervention that saved the program from an early extinction.

Eisenbud's "autoradiobiography" is a most enjoyable piece of work—solid, interesting, and well documented. I warmly recommend it, not only to those familiar with the man himself, but also to everyone interested in the beginnings of the environmental era, and in the role of science, rational administration, and good sense in the solution of the many environmental health problems we have been and continue to be faced with.

— J.W. Thiessen

Editor's note: We intend to publish passages of Eisenbud's book concerning his and ABCC's involvement in the Fukuryu Maru (Lucky Dragon) *incident in a future issue of* Update.

Death Rates for Selected Causes by Dose and Age at Exposure

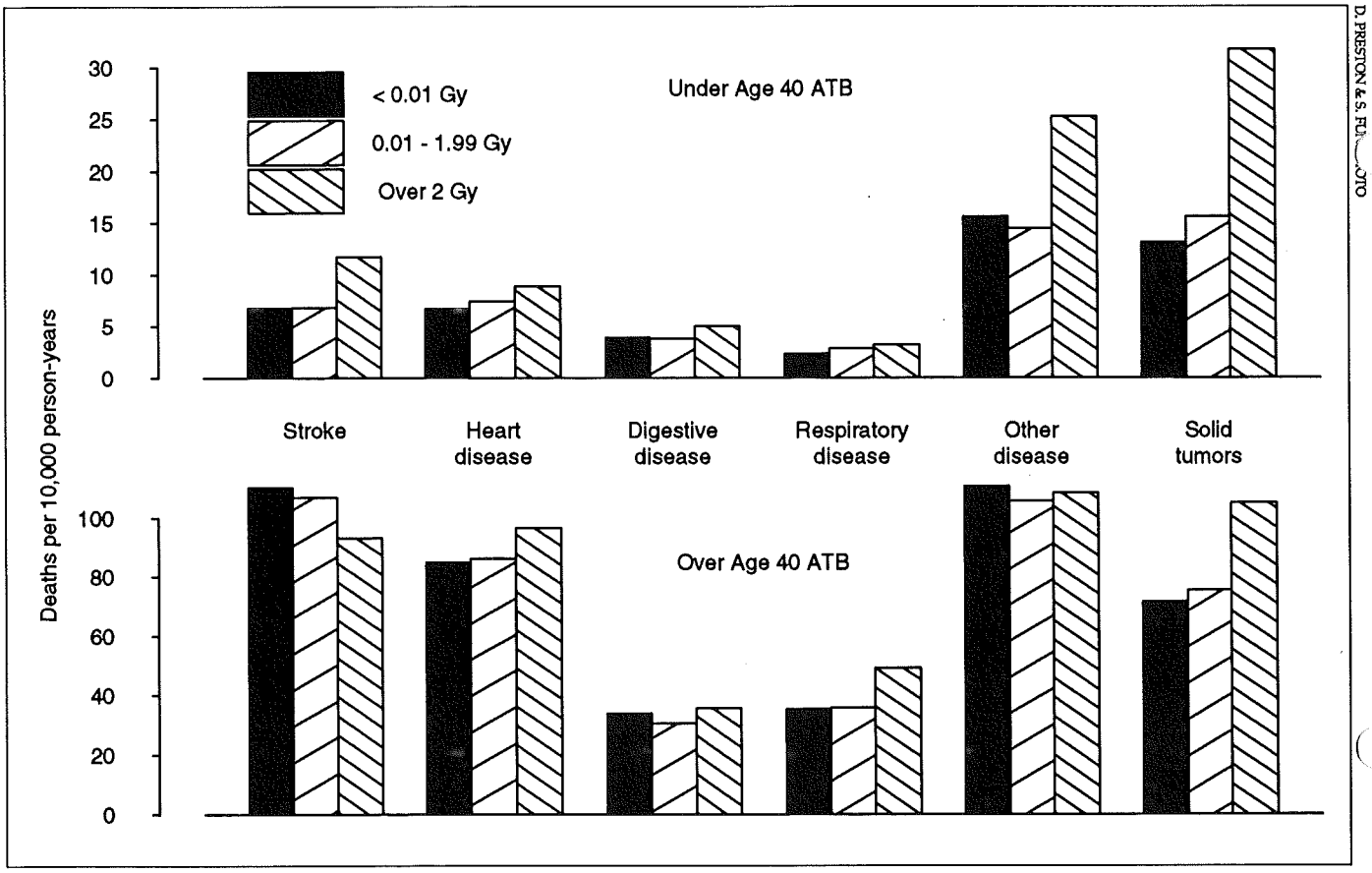
Three articles in this issue of *RERF Update* deal with recent work on noncancer mortality in the RERF Life Span Study (LSS). The figure below summarizes death rates in the LSS for selected causes averaged over the period from 1950 through 1989.

Death rates are based on 86,572 LSS members, who were in Hiroshima or Nagasaki at the time of the bombing (ATB). The under 40 age-ATB population includes 58,586 persons with an average follow-up of 35 years per person. The over 40 age-ATB population includes 27,982 persons with an average follow-up of 20 years per person. Of the LSS members included in this analysis, 41% (18% of those who were under age 40 ATB and 89% of those over age 40 ATB), or 35,289 persons, died during the period from 1950 through 1989.

For each disease category, crude rates are given for three DS86 kerma groups: <0.01 Gy, 0.01–1.99 Gy and ≥2.00 Gy. The last group consists of only a little more than 1% of the total person-years (about 28,000 person-years for those under age 40 ATB and about 5,900 for those over age 40 ATB). For the lower dose categories, the person-year totals are about equal.

The disease category "other" includes all the noncancer cases other than stroke, heart, digestive, and respiratory diseases. Death rates due to leukemia have been omitted.

In looking at these figures, it is important to note the difference in scale for the two age-ATB groups. ❑



Use of RERF Data by Outside Researchers Further Outlined

by Yutaka Hasegawa
RERF Permanent Director

Entrusted with maintaining the confidentiality of atomic bomb survivor data (such as health records and radiation dose estimates) while ensuring their accessibility for research purposes relevant to the survivors themselves or for broader humanitarian purposes, RERF's Operating Committee has approved the following guidelines for use of data by researchers who are based outside of RERF but are collaborating in studies with full-time RERF professional staff through an approved research protocol.

◆ Access to personal health and physical data of the survivors is restricted to use within RERF. To protect the survivors' privacy, such data must not be removed from RERF, except in the form of aggregate tables or figures, i.e., "nonindividual" data, or as nonpersonal data necessary for statistical analyses.

◆ Results of collaborative studies conducted through an approved RERF research protocol will be processed as an RERF technical report, regardless whether the results will be published in the scientific literature.

◆ When the results of collaborative studies using RERF data are presented orally or published, the source of the data should be acknowledged.

Researchers wishing to collaborate in RERF studies must keep in mind that the atomic bomb survivors do not condone the release of their personal information to outside persons or agencies without their (or their legal representatives') express permission. ❑

Recent Scientific Publications

Approved Technical Reports

Life Span Study Report 11, Part 3. Noncancer mortality in the years 1950–85 based on the recently revised doses (DS86). Y Shimizu, H Kato, WJ Schull, DG Hoel. **RERF TR 2-91.**

Deaths in the RERF Life Span Study (LSS) sample have been determined for the years 1950–85 and an analysis of cancer mortality using the revised DS86 doses has been described separately (LSS Report 11, Parts 1 and 2). In this report we examine the relationship to dose of deaths from all diseases other than cancer.

Although the evidence is still limited, there seems to be an excess risk from noncancer death at high doses (2 or 3 Gy and over). Statistically, a pure quadratic or a linear-threshold model (the estimated threshold dose is 1.4 Gy [0.6–2.8 Gy]) is found to fit better than a simple linear or linear-quadratic model. This increase in noncancer mortality is statistically demonstrable, generally, after 1966 and among the younger survivors at the time of the bombing (<40), suggesting a sensitivity for this age group. For specific causes of death, an excess in relative risk at the high dose level, that is, 2 Gy or more, is seen in circulatory and digestive diseases. The relative risk is, however, much less than that for cancer.

These findings, based as they are on death certificates, have their limitations. Most significant, perhaps, is the possible erroneous attribution of radiation-related cancer deaths to other causes. At present, the contribution such errors may make to the apparent increase in noncancer deaths at the higher doses cannot be estimated as rigorously as is obviously desirable. However, even now, this increase does not appear to be fully explicable in terms of classificatory errors.

Further follow-up of mortality in this LSS cohort as well as disease revealed by the biennial physical examinations of the morbidity subsample (the Adult Health Study) of the LSS cohort will be needed to confirm this suggestion of a radiation-related increase in mortality from causes other than cancer, and to determine whether it results in a demonstrable life-shortening among the heavily exposed A-bomb survivors.

Development of a flow-cytometric HLA-A locus mutation assay for human peripheral blood lymphocytes. J Kushiro, Y Hirai, Y Kusunoki, S Kyoizumi, Y Kodama, A Wakisaka, A Jeffreys, JB Cologne, N Nakamura, M Akiyama. **RERF TR 3-91.**

A flow-cytometric technique was developed to measure the frequency of mutant lymphocytes lacking expression of human leukocyte antigen (HLA) A2 or A24 allele products among donors heterozygous for HLA-A2 or A24.

It was found that the mutant frequency of lymphocytes in peripheral blood was on the order of 10^{-4} and increased with donor age. Molecular analyses of mutant clones revealed that about one-third were derived from somatic recombinations and that the remaining two-thirds did not show any alterations after Southern-blotting analysis. A small-scale study on atomic bomb survivors did not show a significant dose effect.

An in vitro mutagenesis study showed that the mutant frequency at the HLA-A24 locus increased at a rate of roughly 2×10^{-4}/Gy, about 10 times greater than that reported at the X-chromosomal hypoxanthine phosphoribosyltransferase locus in lymphocytes. These mutants were found to be mostly derived from large chromosomal deletions.

The effect of diagnostic misclassification on noncancer and cancer mortality dose response in the RERF Life Span Study. R Sposto, DL Preston, Y Shimizu, K Mabuchi. **RERF TR 4-91.**

We performed analyses of cancer and noncancer mortality in the RERF Life Span Study (LSS) to determine whether the observed increased risk of noncancer death due to radiation exposure could be attributed solely to misclassification of causes of death on death certificates. Cancer and noncancer misclassification rates and their dependence on age at death were estimated from a series of autopsies performed on LSS participants between 1961 and 1975. The crude misclassification rates were 20% for cancer and 2.8% for noncancer. Although the noncancer dose response remained significant, correcting for this amount of misclassification reduced the estimated noncancer excess relative risk (ERR) at a 1-Gy exposure by 21% and the number of excess noncancer deaths in the cohort by 23%. The estimated cancer ERR at 1 Gy was increased by 12% and the excess cancer deaths by 16% as a result of the correction. The statistical significance of the noncancer dose response was relatively insensitive to underestimating the cancer misclassification rate, but sensitive to assuming that cancer misclassification was positively associated with dose.

We discuss implementation of the EM algorithm for adjusting for misclassification, and extensions of the method to more than two causes of death.

Thyroid cancer incidence among atomic bomb survivors in Hiroshima and Nagasaki, 1958–79. S Akiba, J Lubin, H Ezaki, E Ron, T Ishimaru, M Asano, Y Shimizu, H Kato. **RERF TR 5-91.**

One hundred and twelve cases of thyroid cancer diagnosed during the period 1958–79 among the extended Life Span Study cohort in Hiroshima and Nagasaki were studied. There was a statistically significant association between thyroid cancer incidence and exposure to atomic bomb radiation. The adjusted excess relative risk (ERR) per gray was 1.1 (95% confidence interval = 0.3; 2.5) and the adjusted absolute risk per 10^4 Gy was 0.59 (95% confidence interval = 0.2; 1.7). Based on a comparison of the deviances obtained from relative and absolute risk models, a simple linear relative risk model appeared to fit the data better than an absolute relative risk model, however, it would not be appropriate to conclude that the data conform strictly to a relative risk pattern.

The incidence of thyroid cancer among the members of the Adult Health Study (AHS) population, who have been medically examined biennially at the RERF clinics since 1958, was 70% higher than that among the rest of the extended LSS cohort after adjustments for city, sex, log age, calendar year, and DS86 dose. There was no significant difference between the slope of the dose-response curve for AHS and non-AHS participants, although the estimated ERRs at 1 Gy for the AHS and non-AHS populations were 1.6 and 0.3, respectively. The elevated risk appeared to be confined to women, and there was an increasing risk with decreasing attained age at exposure.

Measurement of $CD4^-8^-$ T cells bearing T-cell receptor αβ chains by flow cytometry: I. Results for a normal population including two cases with unusually high frequencies. Y Kusunoki, Y Hirai, S Kyoizumi, M Akiyama. **RERF TR 6-91.**

Detection of rare, possibly abnormal, T cells bearing CD3 surface antigen and T-cell receptor αβ chains but lacking both CD4 and CD8 antigens (viz., TCR $\alpha\beta^+CD4^-8^-$ cells as determined by flow cytometry) was performed. The TCR $\alpha\beta^+CD4^-8^-$ T cells were detected at a mean frequency of 0.63 ± 0.35% (mean ± standard deviation) in peripheral blood TCR $\alpha\beta^+$ cells of 119 normal individuals. Two unusual cases besides the 119 individuals showed extremely elevated frequencies of TCR $\alpha\beta^+CD4^-8^-$ T cells, viz., approximately 5% to 10% and 14% to 19% in whole TCR $\alpha\beta^+$ cells. Both were males who were otherwise physiologically quite normal with no history of severe illness, and these high frequencies were also observed in blood samples collected 2 or 8 years prior. The TCR $\alpha\beta^+CD4^-8^-$ T cells of the two individuals were found to express mature T-cell markers such as CD2, 3, and 5 antigens as well as natural killer (NK) cell markers, viz., CD11b, 16, 56, 57 antigens when peripheral blood lymphocytes were subjected to three-color flow cytometry. Lectin-dependent or redirected antibody-dependent cell-mediated cytotoxicities were observed for both freshly sorted and TCR $\alpha\beta^+CD4^-8^-$ cells and in vitro-established clones. Nevertheless, NK-like activity was not detected. Further, Southern blot analysis of TCR β and γ genes revealed identical rearrangement patterns for all the TCR $\alpha\beta^+CD4^-8^-$ clones established in vitro. These results suggest that the TCR $\alpha\beta^+CD4^-8^-$ T cells from these two men exhibit unique characteristics and proliferate clonally in vivo.

continued on next page

Recent Scientific Publications

Approved Research Protocols

Studies of salivary gland tumors among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950–87. T Saku, Y Hayashi, O Takahara, M Tokunaga, S Tokuoka, K Mabuchi, M Soda, E Ron, DL Preston, CE Land. **RERF RP 1-91.**

The incidence of major and minor salivary gland tumors (benign and malignant) diagnosed between 1950 and 1987 will be studied within the RERF Extended Life Span Study sample. Tumors will be ascertained from the tumor and tissue registries in Hiroshima and Nagasaki as well as autopsy files, surgical files, and death certificates maintained by RERF and other major medical institutions. Analyses regarding the shape of the dose-response curve, age at exposure, sex, temporal patterns, and histological type will be conducted.

Studies on skin cancer incidence among the RERF Extended Life Span Study cohort, Hiroshima and Nagasaki, 1950–87. M Kishikawa, T Kobuke, M Iseki, N Sadamori, S Yamamoto, M Soda, M Tokunaga, S Tokuoka, K Mabuchi, E Ron, DL Preston, CE Land. **RP 2-91.**

The skin appears to be more sensitive to the carcinogenic effects of ionizing radiation than has previously been thought. The proposed study will be the first to evaluate skin cancer incidence within the RERF Extended Life Span Study sample in Hiroshima and Nagasaki. Tumors will be ascertained from the tumor and tissue registries in Hiroshima and Nagasaki, as well as from autopsy and surgical record files and from death certificates maintained by RERF and other major medical institutions. Special efforts will be made to obtain cases diagnosed at private dermatology clinics. Analyses regarding the shape of the dose-response curve, age at exposure, sex, temporal patterns, and histological type will be conducted.

Publications in the Open Literature

The observed relationship between the occurrence of acute radiation effects and leukemia mortality among A-bomb survivors. K Neriishi, DO Stram, M Vaeth, S Mizuno, S Akiba. *Radiat Res* 125:206–13, 1991. (RERF TR 18-89)

Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. JD Boice, DL Preston, FG Davis, RR Monson. *Radiat Res* 125:214–22, 1991.

Aging factors and cardiovascular dimensions: a longitudinal study. F Mihara, T Fukuya, H Nakata, S Mizuno, WJ Russell, Y Hosoda. *Radiat Med* 7:271–3, 1991. (RERF TR 16-88)

Radiation-induced skin carcinomas of the head and neck. E Ron, B Modan, DL Preston, E Alfandary, M Stovall, JD Boice. *Radiat Res* 125:318–25, 1991.

Current status of cytogenetic procedures to detect and quantify previous exposures to radiation: a summary. MA Bender, AA Awa, AL Brooks, HJ Evans, PG Groer, LG Littlefield, C Pereira, RJ Preston, B Wachholz. *Health Phys* 60 (Suppl):3, 1991.

Is interindividual variation of cellular radiosensitivity real or artifactual? N Nakamura, R Sposto, J Kushiro, M Akiyama. *Radiat Res* 125:326–30, 1991. (RERF TR 15-89)

The shape of the cancer mortality dose-response curve for the A-bomb survivors. DA Pierce, M Vaeth. *Radiat Res* 126:36–42, 1991. (RERF TR 7-89)

Serum ferritin and stomach cancer risk among a Japanese population. S Akiba, K Neriishi, WJ Blot, M Kabuto, RG Stevens, H Kato, CE Land. *Cancer* 67:1707–12, 1991. (RERF TR 14-89)

Analysis of time and age patterns in cancer risk for A-bomb survivors. DA Pierce, M Vaeth, DL Preston. *Radiat Res* 126:171–86, 1991. (RERF TR 21-89)

Notice regarding Update's *'Looking Back' feature:*

Due to the importance of material relevant to Life Span Study Report 11, Part 3, historical articles on ABCC Director George Darling by Hiroshi Maki and Kenji Joji will be published in an upcoming issue.

Publications of Interest Using RERF Data

A comparison between the risks of childhood leukaemia from parental exposure to radiation in the Sellafield workforce and those displayed among the Japanese bomb survivors. MP Little. *J Radiol Protect* 10(3):185–98, 1990.

A comparison of the apparent risks of childhood leukaemia from parental exposure to radiation in the six months prior to conception in the Sellafield workforce and the Japanese bomb survivors. MP Little. *J Radiol Protect* 11(2):77–90, 1991.

Time variations in radiation-induced relative risk and implications for population cancer risks. MP Little, MW Charles. *J Radiol Protect* 11(2):91–110, 1991.

Bomb survivor selection and consequences for estimates of population cancer risks. MP Little, MW Charles. *Health Phys* 59(6):765–75, 1990.

Weighted least squares estimation for Aalen's additive risk model. FW Huffer, IW McKeague. *J Am Stat Assoc* 86(413):114–29, 1991. ❑

RERF update RERF

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Contributions to *Update* receive editorial review only and are not subjected to scientific peer review. Consequently, the opinions expressed herein are those of the authors only and do not necessarily reflect RERF policies or positions.

Dose and radiation units are given as available in the source material.

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