Keynote Speech

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Dr. Mettler received a B.A. from Columbia University, an M.D. degree from Thomas Jefferson University and Master's Degree in Public Health from Harvard University.
He has authored over 360 scientific publications, including 21 textbooks. He is an Emeritus Commissioner of ICRP, an emeritus member of NCRP and a member of the Nuclear and Radiation Studies Board of the US National Academies. He was the US Representative to UNSCEAR for 28 years. He was the Health Effects Team Leader of the International Chernobyl Project. He has served as an expert on radiology and radiation effects and accidents for the U.S. Department of HHS and Homeland Security, WHO and IAEA. He is currently a health advisor to the Japanese Cabinet for the Fukushima nuclear disaster.

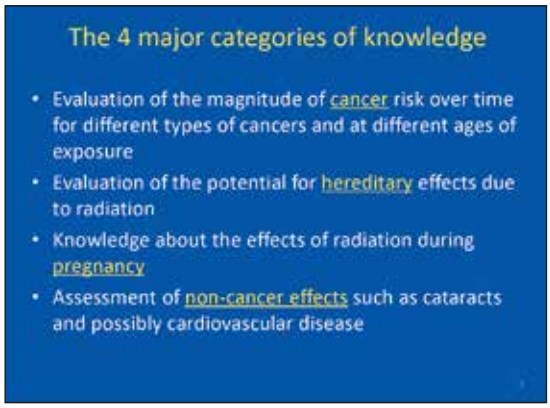
70 years: Learning from Sadako

I would like to thank K. Hiramatsu, K. Kodama, HICARE and the organizers of this symposium for giving me the honor to present the keynote lecture on the occasion of the 70th anniversary of the atomic bombings.

1

Sadako Sasaki is a symbol of innocent victims of war especially children. She died of leukemia as a result of radiation from the atomic bomb in Hiroshima. There were tens of thousands of others who also suffered from radiation effects. My intent is to show how the vast amount of knowledge and expertise that has been accumulated from this tragic event has been effectively used to help other radiation exposed persons having impact upon millions of persons worldwide. It is important to reflect upon this experience especially in light of a confluence of anniversaries in 2015-15 including the 70th anniversary of the bombing, the 40th anniversary of RERF, the 30th anniversary of Chernobyl, the 25th anniversary of HICARE and the 5th anniversary of the Fukushima nuclear accident. It has been aptly pointed out by T. Okubo that the achievements in understanding of radiation effects and the derivative benefits would not have been possible without the cooperation of the participants in the health programs.

There are 4 general categories of health effects that have emerged from studies of atomic bomb survivors including potential hereditary effects, cancer induction, effects on pregnancy and non-cancer effects (such as cataracts and possibly cardiovascular disease). There has been a shift over time in the realization of the effects and focus of the studies. The early period from 1945 to about 1960 dealt primarily with acute effects and genetic effects. By the 1960's there was a realignment in focus with the realization that radiogenic cancer was likely the major long term effect. In the period 1970-2000 and with the creation of RERF, evaluation of specific cancer types, statistical analysis modeling and risk over time was studied. After 2000 there was additional interest and evaluation of non-cancer mortality and effects.



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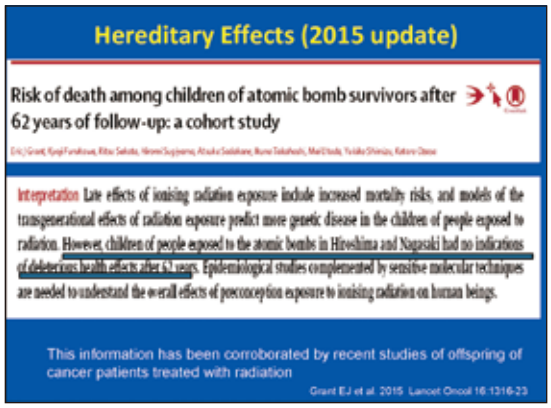
By the mid and late 1960's it had become clear that genetic effects did not seem to be occurring. In spite of this RERF has continued to study the risk of death among children of atomic bomb survivors. A 2015 publication by Grant et.al. with 62 years of follow-up concluded that there was no indication of deleterious health effects in the offspring. This finding has been corroborated by other long term studies of the offspring of cancer patients treated with radiation as children. Lack of evidence however is not evidence of no effect and such effects may take generations to appear. The fact that there has been no identifiable hereditary risk is an important and comforting fact for millions of radiation workers and other exposed persons who have had, or are planning to have, children.



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The RERF data with the associated sophisticated statistical analysis have been crucial to the understanding of radiation-induced cancer. The LSS and AHS are regarded as the gold standard epidemiological studies of radiation effects. The data show that there is a statistically significant excess of cancer which increases almost linearly at doses above about 150 mGy and up to about 3 Gy (Figure 4). At very low doses, the data is not statistically powerful enough to be sure whether there is a cancer risk which is too small to detect (my opinion) or perhaps no risk.

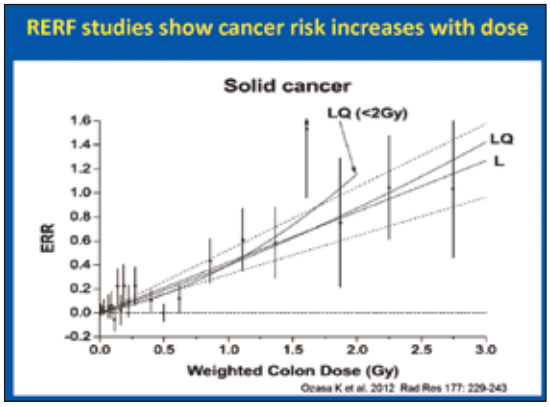

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Figure 4. Increase in excess relative risk (ERR) of mortality with increasing radiation dose (Ozasa et.al. Rad. Res. 177:229-243, 2012). Trend estimates provided for linear (L) and linear quadratic models. Black circles represent ERR for dose categories with vertical lines sowing 95% confidence intervals.

The data of Ozasa et.al. published in 2012 also indicate how much excess cancer mortality was due to the bombing. The LSS data through 2003 has a cohort of 86,111 subjects and there were 50,620 total deaths of which 10,929 (22%) were due to solid cancer and an estimated 527 (1%) excess solid cancer deaths due to radiation. This is a much smaller percentage than is typically assumed by the public.

The RERF data has partially clarified the risk of cancer at different ages of exposure and at different times after exposure. Full characterization will require complete follow-up of all the subjects in the cohort over the next 2-3 decades. It has become apparent that after a latent period, the risk of some radiation caused cancers increases throughout lifetime, while for other neoplasms the risk is relatively stable and for a few (such as leukemia) the risk decreases or even disappears after a few decades (figure 5). This information has been extremely important for many people who have been radiation exposed. As an example, the risk of radiation induced leukemia among children exposed during Chernobyl has essentially passed (since the exposure occurred 30 years ago).

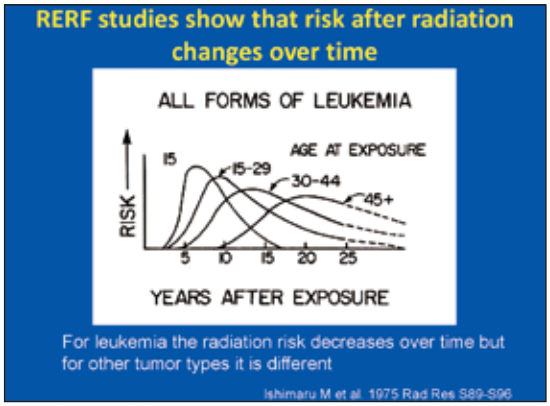

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Figure5. Schematic representation of induction period and risk of leukemia as a function of age at exposure (Ishimaru et. al J Radiat Res.16[Suppl]:S89-96 1975). The curves show that at young age of exposure, leukemia risk peaks at about 5-10 years later (as was the case with Sadako).

One of the most interesting findings is that the risk of radiation-induced cancers in different tissues is quite variable (figure 6). Most people incorrectly think that all types of cancer are equally caused by radiation. It can be seen that bladder, breast and lung tissue are relatively susceptible to radiation caused cancer while there is no significant excess of prostate, uterine or renal cell cancer after radiation exposure. This information has been critical for assessment of causation among the many cases of cancer that occur in workers and other exposed individuals years after radiation exposure.

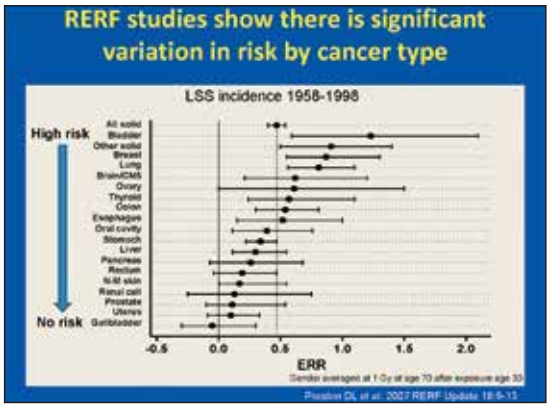

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Figure 6. LSS cancer incidence data clearly show that there is a great variation in the sensitivity of various tissues to radiogenic cancer induction (Preston et.al. RERF Update 2007)

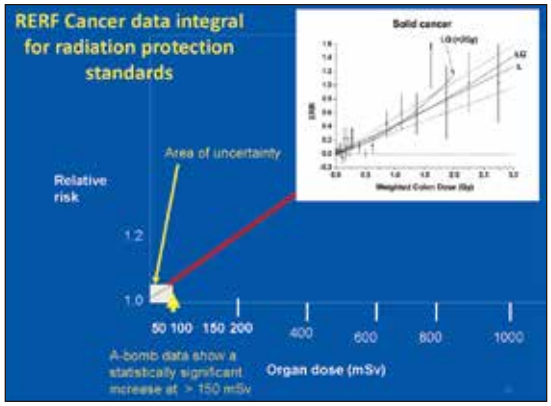
The radiation expertise of Japanese scientists and physicians is recognized worldwide and their involvement has impacted hundreds of thousands of people. For example, the International Chernobyl Project (which took several years) was headed by Dr. I Shigematsu of RERF and there were many Japanese team members who worked evaluating conditions in highly contaminated areas (figure 7).

7

With the generous financial support of Mr. Sasakawa, Japanese scientists conducted another very large 5 year study which was the most complete thyroid evaluation ever done of the more than 160,000 children exposed from Chernobyl.

Major international consensus scientific reports on radiation sources and effects are published periodically by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Virtually every report since 1957 has relied on atomic bomb survivor data and the committee has benefitted greatly from having had I. Tsukamoto, T. Kumatori, Y. Sasaki and Y. Yonekura as officers of the Committee and the input of the Japanese scientific delegations. The most recent report of UNSCEAR included an evaluation of the radiation doses and potential radiation impact of the Fukushima Daiichi Nuclear Power Plant Accident.

When a consensus on radiation effects is reached, another group, the International Commission on Radiological Protection (ICRP), reviews the data and then recommends pubic and occupational dose limits to the international community. Since cancer has been the major long term health issue, the RERF data is the main pillar upon which the recommendations are made. This has been true since the 1960's. A particular example of the influence of RERF data can be seen in the 1990 recommendations of the Commission. At that time the Commission (which included I. Shigematsu) recommended that the annual dose limit to the public be reduced from 5 mSv to 1 mSv. This was primarily based on the emerging RERF data that showed increased sensitivity to cancer induction when a person was exposed as an infant or child. Obviously, this RERF data causing a reduction in the recommended annual public dose limit has had an impact on hundreds of millions of people to date and even more in the future.



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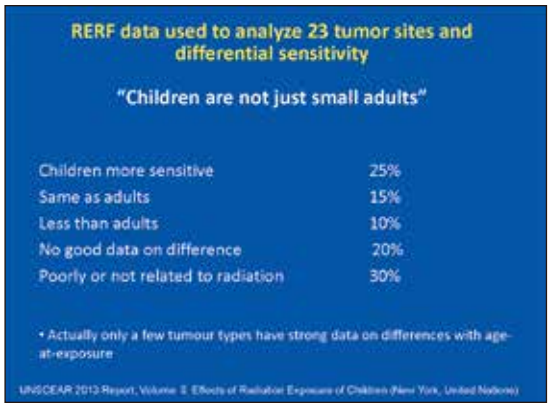
The popular wisdom over the last few decades was that children are about 3 times more sensitive to radiogenic cancer induction than are adults. Recently, the issue of radiation effects on children was reexamined by a Task Group of UNSCEAR. By using the RERF data summarized by R. Shore it became clear that the situation regarding radiation effects on children is not straightforward and depends to some extent on the statistical models used. The results are shown below (figure 9) and indicate that findings from exposed adults cannot directly be used to assess risk from exposure at young ages.



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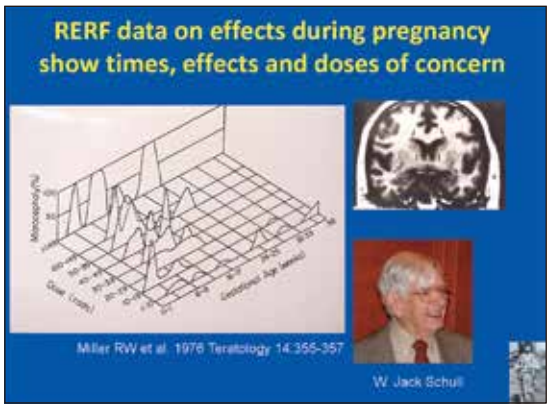
The biodosimetry techniques that have been employed and advanced at RERF have found wide usage around the world. They have been used to estimate doses in the reactor workers at Chernobyl, in management of patients in the Tokaimura criticality accident as well as in many other accidental and epidemiological investigations.
The study of cataracts in a-bomb survivors published by Choshi et.al showed that cataracts can occur a much lower doses than previously thought. This information has now been corroborated in studies of other groups and has particular relevance to the thousands of cardiologists and interventional radiologists who perform fluoroscopically



10

guided procedures each year. In addition, this RERF data has resulted in the ICRP recommending lower international occupational dose limits for the lens of the eye.

Radiation effects on the fetus are a major concern of both workers and the public after radiation exposure. The data from RERF clearly show that there are effects on the brain and intelligence level at high doses and in the period 8-25 weeks of pregnancy. The data also show that at low doses and other times of pregnancy no effect can be detected (figure 10). This information has proven crucial in counselling the many pregnant women who have been exposed either during medical procedures or during accidents (such as Fukushima). Without this information there would likely have been tens of thousands of unwarranted pregnancy terminations around the world.

Figure 10. Incidence of small head size (microcephaly) at various dose levels and gestational ages at exposure (Miller et.al. Teratology 14:355-357, 1976). It can be seen that at high doses of 1 Gy and higher received early in pregnancy the incidence approaches 100% but at lower doses and later in pregnancy there appears to be little or no effect.

Evaluation, health care management and predicted heath risk of the persons exposed during the Fukushima Daiichi Nuclear Power Plant Accident is based largely upon environmental measurements, modelling and RERF/Chernobyl data. This data has been used by the faculty at Fukushima Medical University to design and begin to conduct health studies. The issue of an apparent increase in thyroid cancer incidence at early age and issues with thyroid cancer detection and diagnosis was portended by the finding of occult sclerosing thyroid cancers among the A-bomb survivors. I would also like to add a note that in 2014, heath recommendations of an International Advisory Committee on Fukushima were delivered to Prime Minister Abe and the recommendations were to some extent based on the experience of the a-bomb survivors.

The benefits of the A-bomb data extend now and into the future to untold thousands of people through HICARE outreach and training programs. With all the immense knowledge base and experience that RERF has accumulated in the past 40 years, what remains to be done ? Both O. Niwa and R. Ullrich who both recently arrived at RERF have several significant tasks. Many atomic bomb survivors remain alive and the life-long follow-up will not be complete for 2-3 decades. This information is required to complete the picture of cancer and other risks. There is an issue of what to do with tissue samples that have been obtained and whether any new technologies (such as genomics) can be usefully applied. There is always the continuing issue of budget issues especially when government administrators do not fully understand the impact and remarkable nature of RERF work. Finally there is the important issue of non-cancer mortality.

By the early 1990's researchers (Wong et.al.) at RERF reported that there was a dose related increase in non-cancer diseases and mortality. These findings were further elucidated in a 2004 publication (Yamada et.al.).The work has been carried on with recent publications by Shimizu et. al. and Ozasa et al. In summary there appears to be an increase in mortality from both cardiovascular disease and respiratory diseases. The matter regarding cardiovascular disease is especially complicated due to major risk factors other than radiation and confounding factors (such as diet, smoking, obesity, genetics etc). In addition there have been changes over time in advancing diagnostic methods, disease coding, accuracy of death certificates, diagnostic criteria and medical treatment. At a 2013 RERF workshop it was clear that the various types of cardiovascular disease did not all display the same risk from radiation and in addition many of the conditions have different underlying pathology and etiology. For example, rheumatic heart disease was increased but only in the 1950-1968 period, cardiac failure deaths were increased but mostly in the 1980-1990's and there was no increase in ischemic heart disease or myocardial infarction. Thus more work is required on these topics that potentially could affect millions of people and future radiation protection standards.

I would like to express a note of gratitude to the Japanese news media who are remarkably well-informed about radiation matters and who always have been gracious to me and who have reported my

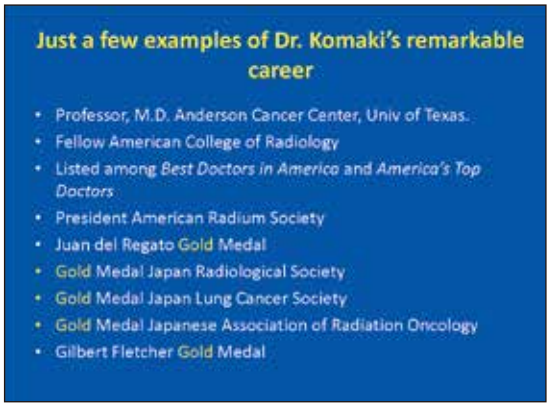
views accurately.

It is only recently that I became aware of a remarkable and inspirational story involving Dr. Ritsuko Komaki in which Sadako's legacy has been directly carried on for over 60 years. Dr. Komaki was a running mate in track with Sadako at elementary school and during her illness Dr. Komaki helped her fold the paper cranes. When Sadako died Dr. Komaki helped start the fund raising for the "Statue of AB Children". Wanting to help sick patients like Sadako, Ritsuko entered Hiroshima University School of Medicine and worked at ABCC (RERF) in the summertime. She ultimately went to the leading U. S. cancer center (MD Anderson Cancer Institute) and became one of the country's leading specialists. As part of her remarkable career she has been President of the American Radium Society and has received at least 5 gold medals from various professional societies including the Japan Radiological Society and the Japan Lung Cancer Society. Dr. Komaki has been involved with development of radistion therapy here in Hiroshima and is married to Dr. James Cox who is on a councilor of RERF. In her own words Dr. Komaki's motivation is "Many people have lost their lives to radiation, but it can be used to save lives. Until the very end Sadako hoped to recover. My goal is to continue saving lives of children who are battling disease as Sadako did".

11

12

In summary, although it is not widely known to the public, the tragic experience of the atomic bomb survivors (and Sadako) has provided knowledge and a resource that has been used to help counsel hundreds of thousands of radiation exposed persons around the world and which provides the main pillar and foundation for international radiation protection recommendations impacting millions worldwide. In spite of past efforts, more important work still needs to be done



13

As I end this presentation, I would like to note that although nuclear weapons have not been used for over 70 years, it is concerning that there are now more countries than ever, who possess or are developing them. Thus we come back to Sadako and the quote "This is our cry, This is our prayer, Peace in the world".

14