Pediatr Radiol (2002) 32: 232–237
DOI 10.1007/s00247-002-0672-0

Elaine Ron

Ionizing radiation and cancer risk: evidence from epidemiology

Dr. Eric Hall: Dr. Elaine Ron is head of the Radiation Epidemiology Branch at NCI and she is going to talk generally about radiation and cancer risk and the evidence that we have for this from epidemiology.

Dr. Elaine Ron: Since Drs. Hall and Brenner already have discussed some of the issues regarding the conduct of epidemiologic studies at low doses, as well as the atomic bomb survivor studies, I will mainly discuss cancer risks associated with low- to medium-level exposure from medical radiation. Although the meeting concerns CT scans, we do not have epidemiologic data on the carcinogenic risks from exposure to CT scans because they are relatively new and, as Dr. Hall said, the doses are fairly low, so very large populations would need to be studied. But, we do have relevant information on other diagnostic and relatively low-dose therapeutic uses of radiation.

To begin, I would like to point out that most of the radiation in the world comes from radon and other natural sources. However, of the 15% of radiation that is artificial, almost all of it is due to medical radiation. In total, 14% of radiation in the world is attributable to medical radiation.

I am giving a talk today because radiology and radiotherapy have been so successful that patients now live long enough to develop long-term sequelae from their radiation exposure. If you weren't successful at what you are doing, there wouldn't be a problem of long-term health effects. Radiation is an important, in fact a necessary, medical tool, but it also is a carcinogen, and as Dr. Brenner mentioned we need to continually weigh the benefits against the risks.

What do we know about radiation risks? Well, we know a great deal from the A-bomb survivors, but also from epidemiologic studies of medical radiation exposure. As Dr. Hall already said, most cancers can be induced by radiation, there is a linear dose response for solid cancers, and young age at exposure enhances cancer risk. Furthermore, women appear to have a higher relative risk of developing radiation-related cancers. Years ago, it was thought that risk might decline after about 20 or 30 years, but the most recent A-bomb survivor data indicate that the risks persist throughout life. Finally, there may be varying degrees of radiation sensitivity for different cancers or sites, i.e., certain cancers seem to occur following low radiation doses while others tend to occur after high doses. Bone marrow, the thyroid gland, the breast, and the lung appear to be especially sensitive to radiation and are associated with high radiation-related risks.

You all know the many uses of medical radiation, but I'm going to focus on diagnostic radiology and radiotherapy for benign diseases, because exceptionally high doses are used to treat malignant diseases. There is one caveat to that statement. Because radiotherapy is most often directed to a specific organ, and sometimes to a specific location in the organ, there is low-dose scatter to other parts of the body. In other words, when you are treating cervical cancer, for example, the thyroid gland also receives some radiation exposure. Therefore, radiation-related cancers can develop in organs or tissues outside the treatment field.

Why do we need epidemiologic studies? I think the main reason is because they provide the only relevant human data. Epidemiology is used to quantify risk from past exposures, to predict lifetime risks, and to monitor existing treatment practices. For example, in the USA,

Published online: 8 March 2002
© Springer-Verlag 2002

E. Ron
Division of Cancer Epidemiology and Genetics,
National Cancer Institute, NIH, 6120 Executive Boulevard,
Rockville, MD 20852, USA
E-mail: eron@mail.nih.gov
Tel.: +1-301-4966600
Fax: +1-301-4020207

we use the cancer incidence data collected by the National Cancer Institute's SEER program to monitor cancer treatment and the development of subsequent cancers. We also use epidemiology to evaluate new medical procedures. We, therefore, are considering conducting studies to evaluate potential risks associated with potential CT scans. Thus, epidemiologic findings can have an impact on radiology and radiotherapy practice. Physicians are rethinking total-body irradiation for adolescents with Hodgkin's disease because of the increased risks of breast and other cancer demonstrated in epidemiologic investigations.

Although studies of the A-bomb survivors are our "gold standard," there are considerable advantages to studying medically irradiated populations. The main advantage is that radiation doses can be estimated from available radiotherapy records and accurate dose estimates allow us to quantify cancer risk. In addition, medical charts often provide information about other medical problems and risk factors that study subjects might have. Charts also have demographic information that allows patients to be traced to ascertain vital status, to mail a questionnaire, or to request a personal interview. Furthermore, different types of radiation are used in medicine. Thus, the findings regarding the mostly gamma exposure from the A-bomb survivor studies can be augmented by evaluating X-rays, alpha particles, and various other types of radiation. Since partial-body radiation is most often used, there is a chance to evaluate the effects of various doses on different organs and tissues, as opposed to whole-body radiation where all the organs and tissues are about equally exposed. Earlier, somebody brought up the issue of stomach cancer and the large difference in incidence in Japan compared with the USA. If we relied solely on the A-bomb survivor data, it would be hard to predict risk in the USA. Fortunately, the investigations of medical populations conducted in the USA and Europe have enabled us to gain a better understanding of risk in non-Japanese populations. Finally, not all patients with the same disease are treated with radiation, so medical populations often have a built-in potential nonirradiated comparison group.

Medical studies also have a negative side. First, patients' underlying disease or other treatments they receive, e.g., chemotherapy, can influence radiation risks, and it can be very difficult to untangle the role of these different factors. Second, patients generally are under fairly close medical surveillance. Because they come back for follow-up, other diseases are more likely to be detected than in the general population. This means that a nonpatient comparison group can appear to be healthier than the irradiated group due to a lower rate of detected disease. A problem related to partial-body irradiation is that it is difficult to pinpoint the radiation dose to a specific tissue or organ location. For instance, there is an increased risk of brain tumors among people who were irradiated for *tinea capitas*. The dose throughout the brain varied substantially, but the exact location of the brain tumor was not always recorded in medical or pathology records. It, therefore, is not possible to determine the risk related to a specific radiation dose. In the case of total-body radiation, the dose is pretty uniform, so exact tumor location is not crucial.

Over the years, a large amount of data concerning relatively low-dose radiation have been collected from the many epidemiologic studies of patients receiving diagnostic radiologic examinations or radiotherapy. None of them are perfect, not even optimal, but at least the data help form a fairly coherent picture about tumorigenic effects at low doses. The A-bomb survivor data provide indications of what to look for, and most findings from the A-bomb survivors have been observed in the medical studies.

Diagnostic radiation

It is well known that the USA has one of the highest rates of radiologic examinations in the world, despite the limited actual data on the number and patterns of use of diagnostic radiologic exams in this country. In the latest report published by the United Nations on sources of medical radiation exposure [1], there are excellent data from the UK, but very little from the USA. Yet, it was clear from the sparse data, that the USA uses radiologic examinations considerably more frequently than most other western countries. Furthermore, as Dr. Hall and Dr. Brenner mentioned, there has been a large increase in use over time in the USA. From 1980 to 1990, and the latest data in the USA are from 1990, there has been a 31% increase in film use. Diagnostic exams have increased between 20% and 25% and therapeutic use between 25% and 30%.

The data from about 1990 show that around 250 million medical X-ray exams are performed each year in the USA. Although the population of Britain is maybe one-fourth of ours, the number of medical X-ray exams performed in the USA is ten times higher. Per capita use of nuclear medical exams in the USA is also greater than in the UK.

As I mentioned earlier, risks for developing radiation-induced cancers in bone marrow, the thyroid, breast, and lung are particularly high. My presentation today will focus on leukemia, and cancers of the thyroid gland and breast.

Table 1 presents a study done in Sweden by Inskip et al. [2]. Because Sweden has computerized registries of hospital records, cancer incidence data, and vital status data, the investigators did not have to rely on patients remembering their medical history, but could instead link various medical records to find out about previous

diagnostic X-rays among people who did and did not have thyroid cancer. There was no excess risk of thyroid cancer observed in this study. However, this is a study mostly of adult, and the adult thyroid is less radiosensitive than the thyroid of children. Table 2 presents another study of adult diagnostic radiation exposure. This was a record-linkage study performed in an HMO in Oregon and California, so recall bias should not be a problem [3]. The investigators evaluated various cancers – leukemia, non-Hodgkin's lymphoma, and multiple myeloma – in relation to diagnostic procedures. They did not report a lymphoma excess risk, but there were small, significant elevated risks for non-Hodgkin's CLL (1.4) and multiple myeloma (1.3), as well as a trend for myeloma incidence to increase with the number of past diagnostic X-rays.

Scoliosis patients have large numbers of X-rays when they are children or young adults. In this cohort of almost 5,000 scoliosis patients presented in Table 3, most of whom had multiple diagnostic X-ray exams, the mean age at exposure was about 11 years and the mean dose was about 0.11 cGy [4]. A significant breast cancer mortality risk, similar to that observed among A-bomb survivors exposed at the same age, was noted. The scoliosis study suggests that even at relatively low protracted doses, excess breast cancer deaths can occur, possibly because the exposure took place at a time when the breast appears to be especially sensitive to radiation damage.

In China, population-based case-control studies of childhood cancer have been conducted (Table 4). The study presented in Table 4 comprises 642 childhood cancer cases and was conducted in Shanghai [5]. The investigators evaluated preconception, in utero, and postnatal radiation, as well as ultrasound. As you can see, statistically significant increased risks of total cancer and acute leukemia were associated with diagnostic radiologic exams, as well as nonsignificantly elevated risks of brain cancer and lymphoma. Although there always needs to be concern about recall bias in case-control studies relying on self-reported exposure to diagnostic radiologic exams, I don't think it is a major bias in this study. To begin with, a self-reported history of ultrasound examinations was not associated with childhood cancers. Furthermore, in another childhood cancer study that I will shortly discuss, the investigators were able to evaluate recall bias and they indicated that both the cases and the controls underestimated their history of diagnostic X-rays by about 11%. Although doses were not estimated in the Chinese study, there was a trend for leukemia and total childhood cancer risk to increase with an increasing number of prior X-rays.

Table 5 shows the data from a recent population-based case-control study of leukemia and postnatal diagnostic X-rays conducted in Canada. Infante-Rivard and colleagues [6] evaluated close to 500 acute lymphocytic leukemia cases under age 10 and an equal number of controls. The cases were matched to their controls on several characteristics, e.g., education of the family and prenatal radiation exposure. As you can see, there is a rather strong radiation-exposure response, with leukemia risk increasing with the number of X-rays (mostly bone X-rays, very few CT scans). Since doses were not known, the number of X-rays served as a proxy measure of dose.

Table 1. Thyroid cancer risk and diagnostic X-ray exams (*RR* relative risk, *CI* confidence interval; from [2])

	Estimated cumulative doses (cGy)			
	0	> 0–0.2	0.2–0.7	0.7–7.5
Cases	133	116	14	121
Controls	137	14	114	119
RR	1.00	1.05	1.04	1.05
95% CI		0.7–1.5	0.70–1.6	0.73–1.5

Table 2. Hematopoietic cancer risks and adult diagnostic X-rays (*CLL* chronic lymphatic leukemia, *NHL* non-Hodgkin's lymphoma, *MM* multiple myeloma, *RR* relative risk; from [3])

Kaiser-Permanente, Oregon and California, 1956–1982	
565 Leukemias (358 non-CLL)	
318 Non-Hodgkin's;	
208 multiple myeloma	
Various diagnostic procedures	
Exposure data from medical records	
RR[a]:	Non-CLL = 1.4 (0.9–2.2)
	NHL = 0.99 (0.6–1-4.6)
	MM = 1.3 (0.6–3.0); *P*-trend 0.03

[a]2-year lag

Table 3. Breast cancer mortality and diagnostic X-rays for scoliosis (*ERR* excess relative risk; from [4])

4,822 Exposed; 644 nonexposed
Mean age at exposure, 10.6 years
Mean dose, 0.11 Gy
70 Observed cancers; 35.7 expected
ERR at 1 Sv = 5.4 (95% CI = 1.2–14)
Results similar to A-bomb survivors

Table 4. Childhood cancer risks and diagnostic X-ray exams (*OR* odds ratio, *CI* confidence interval; from [5])

Population-based study; Shanghai 1981–1991		
642 cancer cases (< 15 years); 642 controls		
Postnatal diagnostic X-ray exposure risks:		
Cancer	OR	95% CI
Total cancer	1.3	1.0–1.7
Acute leukemia	1.6	1.0–2.6
Brain cancer	1.5	0.8–3.0
Lymphoma	1.3	0.6–22

The investigators analyzed the data using different lag times and covariate adjustments. The results remained virtually the same. As I just mentioned, they found an almost equal number of case and control mothers with underestimated diagnostic exposure. The authors wrote, "Control of dosage does not seem fully achieved for pediatric diagnostic radiation. Children may be receiving radiation at higher doses than previously believed at an age where they are more susceptible to radiation." This statement is particularly relevant for this meeting.

To prevent in utero exposure, pregnant women are no longer X-rayed, but we can learn about low-dose exposure at a susceptible age from the earlier experiences. As Dr. Hall mentioned, Doll and Wakeford [7] published a comprehensive review on the subject of in utero exposure. They noted that several case-control studies reported an increased relative risk of about 1.4 for solid cancers and leukemia following about 10–20 mGy. One concern about all of these studies is the reason women were having the X-ray examinations during pregnancy. It is still unsettled whether the examinations were for routine monitoring or because of some suspected underlying health problem that could have influenced the later development of cancer. I doubt that this issue will ever be resolved satisfactorily, but the authors concluded that the in utero exposure was a real risk.

There is a relevant study that was published after the Doll and Wakeford [7] review. It is the case-control childhood cancer study from Shanghai that I mentioned earlier. I have already presented the results from the analysis of postnatal exposure; Table 6 shows the findings for the in utero exposure. As you can see, the relative risks are somewhat higher than the value of approximately 1.4 estimated by Doll and Wakeford. For all childhood cancer, the in utero risk was about 1.8; however, it rose to 2.1 when abdominal X-rays to the mother were analyzed separately. For acute leukemia, the risk actually went up to 2.4, which is larger than seen in most other studies.

Table 5. Childhood leukemia (*ALL*) risks and diagnostic X-ray exams (from [6])

Population-based, Quebec 1980–1993
491 ALL cases (0–9 years); 491 controls
Mostly bone X-rays

	Exams	OR[a]	95% CI
Results	0	1.00	–
	1	1.08	0.7–1.6
	2+	1.78	1.2–2.6

[a]Excludes X-rays 3 months before diagnosis

Table 6. Medical in utero exposure and cancer risks. Shanghai childhood cancer study (from [5])

Cancer	OR	95% CI
All cancer	1.8	0.9–3.6
Abdominal X-ray	2.1	0.7–7.0
Acute leukemia	2.4	0.5–10.6

Radiation treatment for benign disease

Radiation treatment was used for a variety of benign diseases. The frequency of use of radiotherapy for benign diseases seems to wax and wane. Today, radiotherapy is used less often for benign diseases because of the known long-term deleterious health effects. There are, however, some diseases that are still being treated with radiation. Radioactive iodine remains the treatment of choice for hyperthyroidism, at least in this country. Radiotherapy has been introduced recently as a treatment for some benign brain conditions, e.g., AVM and to prevent restenosis following cardiac surgery.

To better understand the risks associated with radiation exposure to the thyroid gland, seven studies (five cohort and two case-control) with suitable data were pooled [8]. Most of the analyses were based on the five cohorts (children who received radiation for enlarged thymus, *tinea capitas*, various head and neck conditions, in particular enlarged tonsils, childhood cancer, and atomic bomb survivors). Table 7 shows the excess relative risk estimate for each of the studies in [8]. In a study that has a mean dose of about 0.1 Gy, a statistically significant increased relative risk was reported. The point estimates of the risks range quite a bit, but there isn't a very large difference among them when you look at the confidence intervals. When a pooled analysis was conducted, a clear linear dose response was demonstrated for people who were exposed before age 15 (Fig. 1). For those exposed at age 15 or older, no risk was apparent, whereas for the group exposed before age 15, a very steep dose-response was observed. Among the group of people who were less than 15 years old at treatment, there was a strong trend for the risks to increase as the person's age at exposure decreased.

I would like to summarize my presentation by saying that children less than 15 years old had about 10% of all CTs in the USA. That means that over 2 million children per year have CT scans. As you have already heard, the exposure is often greater than it need be. It appears that the bone marrow dose may be about 0.01 Gy, and

Table 7. Thyroid cancer after childhood radiotherapy

Study	Mean dose (Gy)	ERR/Gy
Enlarged thymus	1.4	9.1 (3.6–29)
Michael Reese tonsils	0.6	2.5 (0.6–26)
Israeli *tinea capitis*	0.1	32 (14–57)
Childhood cancer	12	1.1 (0.4–29)
A-bomb survivors (< 15 years)	0.3	4.7 (1.7–16)

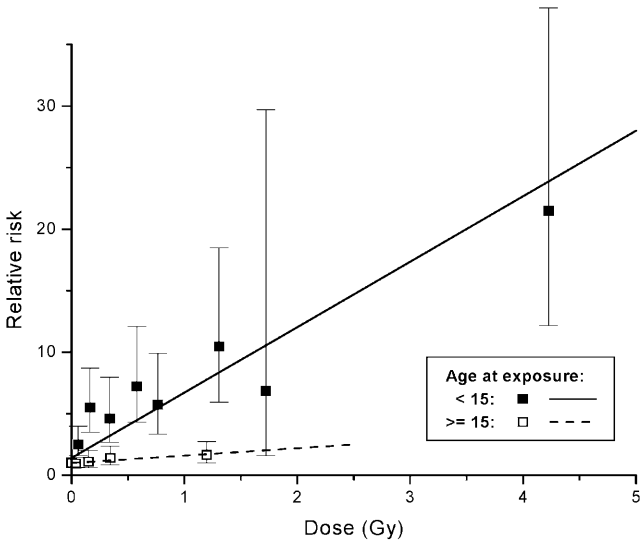

Fig. 1. Relative risk for thyroid cancer by age at exposure

as Dr. Brenner has pointed out, about 30% of these children receive more than three CTs. These are doses that might increase the risk of cancer in some of the exposed children. Radiation in medicine is essential, and should be used when it is needed either for diagnosis or treatment. However, more thought should be given to reducing doses as much as possible, and to potential risks especially when dealing with children.

Questions

Questions: (1) Is there any updated information in the literature about the genetic risks of low-dose radiation? (2) What is the incidence of nonfatal versus fatal cancers, because Dr. Brenner has illustrated a fatal cancer incidence. I would imagine that the nonfatal cases would represent a larger public health issue.

Dr. Elaine Ron: There has been research on genetic risks and radiation in humans, but the data are fairly sparse. In the cohort of atomic bomb survivors, there have been reports about the second generation, i.e., children who have at least one exposed parent. To date, the results have been reassuring – no detectable genetic effects have been observed.

The incidence of nonfatal cancers is much higher than fatal ones, especially as survival is improving. At equal doses, the excess absolute risk for incident cancers is about two times higher than for fatal cancers in the atomic bomb survivors. The radiation risks are higher for the nonfatal cancers partly because thyroid and breast cancers are very radiation sensitive and have relatively good survival.

Question: On the paper that both of you quoted by Doll and Wakeford, I was intrigued by the 40% increase in risk from obstetric X-ray exams, but it sounded like it was more in the third trimester? Do you think there is something different between in utero exposure versus a premature infant or are we seeing some increased risks in the premature population? As we become more and more aggressive with our therapy, is a premature infant at an even higher risk than a 2-year-old or a 5-year-old child?

Dr. Elaine Ron: I don't know. I don't know of any studies of premature babies. In the A-bomb survivors, they have studied the in utero cohort, but it is fairly small. They have found increased risks for mental retardation, and small head size depending on dose and the trimester of the mother's exposure.

Question: Are there any data to clarify whether the risk from a series of low-dose exams is the same or less than an equivalent single dose? Ten 1-mSv doses versus one 10-mSv dose.

Dr. Elaine Ron: There is a fair amount of animal data on fractionated exposure versus acute exposure. These data suggest that fractionated exposure is less carcinogenic than acute exposure. In humans, there are very limited data. The risks of developing breast cancer following acute (A-bomb survivors and high dose-rate radiotherapy) compared with fractionated exposure (patients who received multiple fluoroscopic exams) are similar; however, the results are much less clear for other cancer sites. For lung cancer, there seems to be a difference in risk for fluoroscopy patients compared with the A-bomb survivors. At this time, the human data are not adequate to fully address this issue.

Question: There was a paper in the most recent edition of the *British Journal of Radiology*, again by Sir Richard Doll, who must be pushing 90 by now. It's a 100-year survey of radiologists in the UK. The bottom line is that radiologists who have been practicing for more than 40 years in the UK (started before the 1950s) have a 40% excess relative risk of a fatal malignancy. He went on and made some estimates of the doses that these people received over a lifetime of diagnostic radiology and came to the conclusion that the risk per unit dose in radiologists compared with the Japanese (this is 40 years fractionated dose versus an acute dose) was somewhere between 2 and 7, which is not that different from the 2–10 of the NCRP. Do you have a comment on it?

Dr. Elaine Ron: The results from this study suggest that fractionated radiation exposure is less carcinogenic than the acute exposure received by the A-bomb survivors. It should be noted, however that individual dose estimates are not available for the radiologists and, therefore, only crude comparisons could be made.

References

1. UNSCEAR (United Nations Scientific Committee on the Effects of Radiation) (2000) Sources and effects of ionizing radiation. United Nations, New York
2. Inskip PD, Ekbom A, Galanti MR, et al (1995) Medical diagnostic X-rays and thyroid cancer. J Natl Cancer Inst 87:1613–1621
3. Boice JD Jr, Morin MM, Glass AG, et al (1991) Diagnostic X-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. JAMA 265:1290–1294
4. Doody M, Lonstein JE, Stovall M, et al (2000) Breast cancer mortality after diagnostic radiography: findings from the U.S. Scoliosis Cohort Study. Spine 25:2052–2063
5. Shu XO, Jin F, Linet MS, et al (1994) Diagnostic X-ray and ultrasound exposure and risk of childhood cancer. Br J Cancer 70:531–536
6. Infante-Rivard C, Mathonnet G, Sinnett D (2000) Risk of childhood leukemia associated with diagnostic irradiation and polymorphism in DNA repair genes. Environ Health Perspect 108:405–498
7. Doll R, Wakeford R (1997) Risk of childhood cancer from fetal irradiation. Br J Radiol 70:130–139
8. Ron E, Lubin JH, Shore RE, et al (1995) Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 141:259–277