

## CANCER RISKS FROM MEDICAL RADIATION

Elaine Ron\*

**Abstract**—About 15% of the ionizing radiation exposure to the general public comes from artificial sources, and almost all of this exposure is due to medical radiation, largely from diagnostic procedures. Of the approximately 3 mSv annual global per caput effective dose estimated for the year 2000, 2.4 mSv is from natural background and 0.4 mSv from diagnostic medical exams. Diagnostic and therapeutic radiation was used in patients as early as 1896. Since then, continual improvements in diagnostic imaging and radiotherapy as well as the aging of our population have led to greater use of medical radiation. Temporal trends indicate that worldwide population exposure from medical radiation is increasing. In the United States, there has been a steady rise in the use of diagnostic radiologic procedures, especially x rays. Radiotherapy also has increased so that today about 40% of cancer patients receive some treatment with radiation. Epidemiologic data on medically irradiated populations are an important complement to the atomic-bomb survivors' studies. Significant improvement in cancer treatment over the last few decades has resulted in longer survival and a growing number of radiation-related second cancers. Following high-dose radiotherapy for malignant diseases, elevated risks of a variety of radiation-related second cancers have been observed. Risks have been particularly high following treatment for childhood cancer. Radiation treatment for benign disease was relatively common from the 1940's to the 1960's. While these treatments generally were effective, some resulted in enhanced cancer risks. As more was learned about radiation-associated cancer risks and new treatments became available, the use of radiotherapy for benign disease has declined. At moderate doses, such as those used to treat benign diseases, radiation-related cancers occur in or near the radiation field. Cancers of the thyroid, salivary gland, central nervous system, skin, and breast as well as leukemia have been associated with radiotherapy for tinea capitis, enlarged tonsils or thymus gland, other benign conditions of the head and neck, or benign breast diseases. Because doses from diagnostic examinations typically are low, they are difficult to study using epidemiologic methods, unless multiple examinations are performed. An excess risk of breast cancer has been reported among women with tuberculosis who had multiple chest fluoroscopies as well as among scoliosis patients who had frequent diagnostic x rays during late childhood and adolescence. Dental and medical diagnostic x rays performed

many years ago, when doses were presumed to be high, also have been linked to increased cancer risks. The carcinogenic effects of diagnostic and therapeutic radionuclides are less well characterized. High risks of liver cancer and leukemia have been demonstrated following thorotrast injections, and patients treated with radium appear to have an elevated risk of bone sarcomas and possibly cancers of the breast, liver, kidney, thyroid, and bladder.

Health Phys. 85(1):47-59; 2003

Key words: NCRP; cancer; medical radiation; health effects

## INTRODUCTION

FOR THE year 2000, UNSCEAR (2000) estimated that the annual global per caput effective radiation dose was slightly less than 3 mSv. Although the doses vary worldwide, the greatest contribution, by far, is from natural sources (~85%). Artificial, or man-made, sources account for the remaining ~15% of exposure to the general public. Almost all (~95%) of the man-made exposure is the result of medical radiation, largely from diagnostic procedures. The amount of medical exposure can differ remarkably depending on the level of health care services available. Using the number of physicians per unit of population to categorize level of health care, it has been estimated that the average annual effective dose from medical radiation is as low as <0.02 mSv in populations having only one physician for >10,000 people and as high as 1.2 mSv in populations having one physician for <1,000 people (Table 1) (UNSCEAR 2000).

Although current data on medical exposure to the general public in the United States are scarce, the United States has a relatively high rate of diagnostic x-ray exams (Mettler et al. 1993). In 1991-1996, the annual United States per caput effective dose from diagnostic medical x-ray exams was 0.5 mSv. In several European countries with a high level of health care, such as Germany, France, and Norway, the per caput effective dose was even larger (UNSCEAR 2000).

Radiation was used in the diagnosis and treatment of patients as early as 1896 (Hall 2000). By the 1920's, barium contrast studies were introduced. Since then, continual improvements in medical imaging technology

\* Division of Cancer Epidemiology and Genetics, National Cancer Institute, EPS 7048, 6120 Executive Boulevard, Bethesda, MD 20892.

For correspondence or reprints contact: the author at the above address, or email at [eron@mail.nih.gov](mailto:eron@mail.nih.gov).

(Manuscript received 28 February 2003; accepted 29 March 2003)

0017-9078/03/0

Copyright © 2003 Health Physics Society

**Table 1.** Population exposure to radiation from diagnostic x-ray examinations by level of health care.<sup>a</sup>

Health care level	Total population (millions)	Population per physician	Total number of medical x-ray exams (millions)	Annual number of medical x-ray exams per 1,000 population	Average annual effective dose to population (mSv)
I	1,530	<1,000	1,410	920	1.2
II	3,070	1,000–3,000	470	150	0.14
III	640	3,000–10,000	24 (III + IV)	20	0.02
IV	565	>10,000		<20	<0.02
Worldwide average				330	0.4

<sup>a</sup> Adapted from UNSCEAR (2000).

and radiotherapy as well as the aging of our population have led to greater use of medical radiation. Temporal trends indicate that the worldwide frequency of diagnostic x-ray exams per 1,000 population has increased by about 10% from the period of 1983–1990 to 1991–1996, the mean effective dose per exam by about 20%, and the annual collective dose by close to 50% during the same time periods. In the United States, there has been a steady rise in the use of both diagnostic radiologic procedures and radiotherapy. The decline in the use of pelvimetry as a diagnostic procedure is one exception (UNSCEAR 2000). The treatment of benign diseases with radiation waxes and wanes, largely depending on what other treatments are available, whereas the use of radiotherapy for cancer patients has increased slowly over the last quarter century. In 1975, about 25% of cancer patients registered in the U.S. SEER (Surveillance, Epidemiology, and End Results Program) cancer registry program received radiation as part of their initial treatment course, whereas about 30% of current cancer patients are similarly treated.<sup>†</sup>

Over the last two decades, a wealth of epidemiologic data on medically irradiated populations has been collected. Indeed, Little (2001) recently reviewed 65 epidemiologic studies of irradiated patients, and the latest UNSCEAR (2000) report included almost 50 studies of irradiated patients in its epidemiologic evaluation of radiation-related cancer. One of the unique features of radiation used in medicine is that doses range from up to a few milligray for most diagnostic examinations to many tens of gray for treatment of cancer. Epidemiologic investigations of people receiving medical radiation in the course of diagnosis or treatment have provided quantified information on the level of cancer risk following a broad spectrum of medical practices, and these data are an important complement to the atomic-bomb survivor studies. To gain additional insights into the mechanisms that underlie radiation carcinogenesis, epidemiologic studies of medically irradiated populations are incorporating molecular components when possible. One

advantage for studying patient populations is that they typically have a high study participation rate and are cooperative in agreeing to provide biologic specimens.

This review focuses on radiation risk estimates derived from recent epidemiologic studies of patients who received diagnostic or therapeutic radiation. Although diagnostic exposures are generally low, they involve many millions of people. In contrast, therapeutic exposures are large, but few people are treated. Studies of medically irradiated cohorts exposed to moderate to high doses and with long follow-up are particularly informative. Studies of low-dose or fractionated diagnostic x-ray exposure are more complicated because statistical power is low and the potential influence of bias and confounding is large. Nevertheless, this review highlights investigations of diagnostic radiography because these exposures are of most relevance in terms of public health concerns. Risks by age at exposure also are emphasized because exposure at young age often is more carcinogenic than adult exposure.

## DIAGNOSTIC RADIATION

Table 2 shows the estimated frequency and effective doses of specific diagnostic x-ray examinations performed in countries with the highest level of medical care (UNSCEAR 2000). It can be seen that chest radiography and x rays of the limbs and joints are by far the most common exams, but that computerized tomography (CT) scans, angiography, and interventional procedures have the highest effective dose per exam. Trends in the annual per caput effective dose indicate that although doses gradually have been lowered for routine diagnostic x-ray exams, there has been rapid growth in new highly sophisticated, higher dose procedures, such as helical CT scans. In the United States, diagnostic film use increased by 31% from 1980–1990 (Mettler et al. 1993). Diagnostic examinations increased from 790 x-ray exams per 1,000 population in 1980–1984 to 800 and 962 in 1985–1990 and 1991–1996, respectively. It is estimated that about 250 million diagnostic x-ray exams and an additional 8.2 million nuclear medical examinations are

<sup>†</sup> R. Curtis, personal communication, National Cancer Institute, Bethesda, Maryland.

**Table 2.** Estimated average frequency and effective doses for diagnostic x-ray examinations<sup>a</sup> (1991–1996).<sup>b</sup>

Examination	Exams/1,000 population	Effective dose per exam (mSv)
<b>Medical examinations</b>		
Chest radiography	281	0.14
Chest photofluoroscopy	35	0.65
Chest fluoroscopy	12	1.1
Limbs and joints	166	0.06
Lumbar spine	48	1.8
Thoracic spine	13	1.4
Cervical spine	32	0.27
Pelvis and hip	35	0.83
Head	59	0.1
Abdomen	41	0.5
Upper GI tract	42	3.6
Lower GI tract	9	6.4
Cholecystography	3	2
Urography	12	3.7
Mammography	25	0.5
CT	57	8.8
Angiography	8	12
Interventional procedures	3	20
Total	920	330
Average effective dose per medical x-ray examination (mSv)		1.3
<b>Dental examinations</b>		
Total	310	
Average effective dose per dental x-ray examination (mSv)		0.02

<sup>a</sup> Rounded estimates based on data from a selected sample of countries, having 1 physician per <1,000 people, and responding to the UNSCEAR Survey of Medical Radiation Usage and Exposures.

<sup>b</sup> Adapted from UNSCEAR (2000).

performed each year in the United States. Thus, the United States population has close to one exam per person per year.

It is difficult to evaluate cancer risks associated with diagnostic x-ray examinations using epidemiologic methods for a variety of reasons. Doses are generally low, and estimating individual organ doses is complicated because radiologic records usually can not be obtained. Data regarding diagnostic radiographs often are collected in case-control studies by asking the patient, or sometimes the patients' family, to recall each diagnostic exam the patient had during their lifetime or over a specified period of time. This information typically is elicited during a personal or telephone interview or by mailed questionnaire. Unfortunately, personal recall is imperfect and people cannot always remember all of their past x rays, when they were performed, or what type they were. In case-control studies, the additional problem of recall bias, i.e., cancer patients may remember their medical history better than a control who does not have a serious disease, can result in risk estimates that are artificially high. Nevertheless, some studies are informative, especially when multiple examinations were performed because cumulative doses can reach levels consistent with adequate statistical power.

Systematic follow-up of cohorts of tuberculosis and scoliosis patients who received repeated x-ray exams to monitor treatment provide information on the dose-response relationship for fractionated radiation exposures. Studies of tuberculosis patients who received multiple fluoroscopies, generally as adolescents or young adults, have been especially informative because individual organ doses were calculated with the aid of medical records and phantom experiments (Sherman et al. 1978; Howe and McLaughlin 1996; Little and Boice 1999). Due to the large number of exams patients received, cumulative doses to the chest area reached 0.5–1 Gy. Table 3 shows the risk of developing breast cancer in tuberculosis patients is substantial (Boice et al. 1991a; Howe and McLaughlin 1996). Similar to findings from the atomic-bomb survivors (Thompson et al. 1994), the risk declined with increasing age at exposure, with little risk seen after menopause. In contrast, although doses to the lung were considerable there was no excess risk of lung cancer (Davis et al. 1989; Boice et al. 1991a; Howe 1995), which suggests that the carcinogenic potential of fractionated exposure to the breast does not differ substantially from acute exposure, whereas fractionated exposure to the lung appears to be less carcinogenic than acute exposure. Large and significant excess relative and absolute risks of breast cancer mortality also have been reported among a cohort of 5,573 scoliosis patients who had frequent diagnostic x rays during late childhood and adolescence (Doody et al. 2000). The risk of breast cancer mortality increased significantly with increasing number of x-ray examinations and with increasing breast dose. The dose response was especially pronounced among women who were first exposed between the ages of 10 and 11 y, i.e., about the time of breast budding. Although the radiation exposure was highly fractionated, the excess relative risk (ERR) per gray ( $ERR_{Gy} = 5.4$ ; 95% CI = 1.2–14.1) was not inconsistent with that for female atomic-bomb survivors who were less than age 20 y at the time of the bombings ( $ERR_{Sv} = 3.16$ ; 90% = 1.6–5.0) (UNSCEAR 2000).

Studies of the carcinogenic risks associated with diagnostic radiography during early childhood have generally employed a case-control design and have mainly used childhood cancer patients as the cases (Table 3). Shu et al. (1994) and Infante-Rivard et al. (2000) reported that cases with childhood acute lymphocytic leukemia (ALL) had a higher frequency of prior x-ray examinations than controls. These findings are based on information on past x-ray examinations obtained from interviews conducted with mothers of the cancer patients. In both investigations, attempts were made to evaluate potential recall bias. In the study conducted in China, Shu et al. (1994) also asked questions about ultra sound

**Table 3.** Cancer risks associated with x-ray exposure from diagnostic examinations.<sup>a</sup>

Study	Study design	Study population	Cancer sites studied	Mean organ dose (Gy)	Significant findings
<b>Adult exposure</b>					
<b>Mixed diagnostic x rays</b> US: Kaiser Permanente HMO Boice et al. 1991b	Case control	565 leukemia 318 NHL 208 multiple myeloma 1,390 Controls	leukemia, NHL, multiple myeloma	NA <sup>b</sup>	none
US: Los Angeles Preston-Martin et al. 1988	Case control	408 parotid 408 controls	parotid gland <sup>c</sup>	0.15	ERR <sub>Gy</sub> = 1.65 (0.52–3.4)
Sweden Inskip et al. 1995	Case control	484 thyroid 484 controls	thyroid	NA	none
Sweden Hallquist and Nasman 2001	Case control	180 thyroid 360 controls	thyroid	NA	none
<b>Adolescent exposure</b>					
<b>TB fluoroscopy</b> Massachusetts Boice et al. 1991a	Cohort Incidence	2,367 exposed 2,427 unexposed	breast <sup>c</sup>	0.79	ERR <sub>Gy</sub> = 0.40 (0.2–0.7)
Davis et al. 1989	Cohort Mortality	6,285 exposed 7,100 unexposed	esophagus <sup>c</sup> lung leukemia	0.80 0.84 0.09	ERR <sub>Gy</sub> = 0.53 (–0.22–2.5) ERR <sub>Gy</sub> = –0.19 (<–0.2–0.04) ERR <sub>Gy</sub> = <–0.2 (<–0.2–4.5)
Canada Howe 1995; Howe and McLaughlin 1996	Cohort Mortality	25,007 exposed 39,165 unexposed	breast <sup>c</sup> lung	0.89 1.02	ERR <sub>Gy</sub> = 0.90 (0.55–1.39) ERR <sub>Gy</sub> = 0.0 (–0.06–0.07)
<b>Scoliosis</b> US Doody et al. 2000	Cohort Mortality	4,822 exposed 644 unexposed	breast <sup>c</sup>	0.11	ERR <sub>Gy</sub> = 5.4 (1.2–14.1)
<b>Childhood exposure</b>					
<b>Mixed diagnostic x rays</b> Shanghai Shu et al. 1994	Case control	642 childhood cancer 642 controls	childhood cancer <sup>c</sup> acute leukemia <sup>c</sup> brain cancer lymphoma	NA NA NA NA	OR = 1.3 (1.0–1.7) OR = 1.6 (1.0–2.6) OR = 1.5 (0.8–3.0) OR = 1.3 (0.6–2.2)
Canada Infante-Rivard et al. 2000	Case control	491 ALL <sup>d</sup> 491 controls	ALL <sup>c</sup>	NA	#exams OR 0 1.0 1 1.04 2+ 1.61 (1.1–2.3)
US: Children's Cancer Group Shu et al. 2002	Case control	1842 ALL 1986 controls	ALL pre-B-cell ALL <sup>c</sup>	NA NA	none ??

<sup>a</sup> Adapted from UNSCEAR (2000) and Little (2002).

<sup>b</sup> NA = not available.

<sup>c</sup> Statistically significant at  $p = 0.05$  level.

<sup>d</sup> ALL = acute lymphocytic leukemia.

examinations and found no relation between their frequency and ALL. In Canada, Infante-Rivard and Jacques (2000) validated the frequency of prenatal diagnostic x-ray exams recalled by the mothers of the cases, population controls and hospital controls against hospital medical records. Although mothers of all three groups underreported examinations, the level of underreporting did not differ significantly between the cases and controls. The radiation-related risk was higher when analysis was done using hospital record data compared with using data from mothers' recall, which is consistent with the

diminution of risk generally observed when misclassification is nondifferential. Based on very small numbers of cases and statistically nonsignificant results, data from this investigation suggest that the association between radiation and childhood leukemia may be modified by polymorphisms in DNA repair genes. Two other case-control studies did not find an association between childhood leukemia and past radiation exposure from diagnostic x rays. In a very large study, conducted in the framework of the Children's Cancer Group (Shu et al. 2002), there was little evidence of an association between

childhood leukemia and diagnostic x rays except in a subgroup of children with pre-B-cell ALL. This study, however, did not validate medical records. Meinert et al. (1999) reported no statistically significant difference in the frequency of self-reported diagnostic x rays in a case-control study of childhood cancers conducted in Germany, but the methodologic limitations of this study complicate interpretation of the results. Individual doses were not estimated in any of these investigations, and, therefore, potentially large differences in the dose distributions might partly explain the inconsistent findings.

Most of what is known about adult diagnostic exposure also comes from case-control studies. Relying on information about frequency of past radiographic exams obtained from comprehensive and detailed patient interviews, Preston-Martin and colleagues (Preston-Martin et al. 1988, 1989) reported increased risks of leukemia and cancer of the parotid gland associated with adult exposure to dental and medical diagnostic x rays performed many years ago, when exposure was presumed to be high (Table 3). An earlier validation study of dental x ray recall, conducted by this group (Preston-Martin et al. 1985), found underreporting of equal magnitude in both cases and controls. Little (2001) estimated that the  $ERR_{sv}$  for salivary gland malignancies was 1.65 (95% CI = 0.52–3.40), which is almost identical to his estimate of 1.59 (95% CI = 0.35–3.91) for atomic-bomb survivors. Investigators in Sweden (Inskip et al. 1995, Hallquist and Nasman 2001) evaluated diagnostic x-ray exams and the risk of thyroid cancer using medical records to determine an almost complete and unbiased exposure history for all cases and controls. Neither of these studies reported an association, but most of the exposure occurred during adulthood, and there is little evidence linking adult radiation exposure to thyroid cancer development (Thompson et al. 1994; Ron et al. 1995). In a study conducted in Kaiser-Permanente, the difference in the frequency of diagnostic x rays performed in 1,091 adults with hematopoietic malignancies and 1,390 controls was not statistically significant (Boice et al. 1991b). Individual doses were not available, but the mean number of x rays was about 12 and about 12% of the diagnostic exams were high-dose fluoroscopies or multafilms. The authors estimated that the dose from 5–14 x rays ranged from 0.1–50 mGy.

Stewart et al. (1956) first reported that diagnostic exposure of the fetus to radiation in utero increased the risk of childhood cancer and leukemia about twofold. This study (Oxford Survey of Childhood Cancers) was later expanded to include over 15,000 childhood cancer cases, diagnosed between 1953–1981, and an equal number of controls. With the additional years of case accrual, the risks decreased to about 1.4, possibly due to

the reduction over time in exposure to pregnant women from diagnostic exams (Knox et al. 1987). Most other case-control studies of radiation exposure of the fetus from diagnostic in utero exams report increased risks of about 1.4 for solid cancers and leukemias at doses of about 10–20 mGy (UNSCEAR 1994). Doll and Wakeford (1997) reviewed all published studies evaluating risk of childhood cancer following in utero radiation exposure and they concluded that fetal exposure of about 10–20 mGy increases the risk by about 40%. While there is been some controversy regarding the causal nature of this relationship (Boice and Miller 1999), taken as a whole the data suggest that low doses of in utero exposure increase the risk of childhood cancer although the magnitude of the risk is uncertain (UNSCEAR 2000). Studies published lately (Naumburg et al. 2001; Shu et al. 2002) are reassuring because they suggest that more recent lower in utero exposure does not appreciably increase the risks of childhood cancer.

The carcinogenic effects of internally-deposited diagnostic radionuclides are not well characterized. Thorotrast is an alpha-emitting contrast medium that was used throughout the world between the late 1920's and early 1950's for a variety of diagnostic procedures. It has a half-life of about 400 y, and since it is hardly excreted from the body, patients were exposed to radioactivity throughout their life. Epidemiologic follow-up studies of thousands of patients injected with Thorotrast consistently show high risks of liver disease, cancer, and leukemia (dos Santos Silva et al. 1999; Mori et al. 1999; van Kaick et al. 1999; Travis et al. 2001; Nyberg et al. 2002). The elevated risks persisted for 40 y or more. Furthermore, patients exposed to Thorotrast had a significantly higher number of chromosomal aberrations than nonexposed patients (Platz et al. 2000). Diagnostic examinations with  $^{131}I$ , a low-LET radionuclide that concentrates in the thyroid gland and has a half-life of about 7–8 d, have not been linked convincingly with thyroid cancer (Hall et al. 1996; Hahn et al. 2001) or any other malignancy (Holm et al. 1989). The radiation doses from diagnostic  $^{131}I$  exams are extremely small to most organs and tissues, but the mean dose to the thyroid was about 1 Gy in a cohort study of almost 35,000 Swedish patients receiving  $^{131}I$  exams (Hall et al. 1996). One possible reason for the negative thyroid findings in the Swedish study is that almost all of the patients evaluated were exposed as adults and none were young children. In the German study (Hahn et al. 2001), although the patients were children, the median age of the exposed subjects was 14.9 y and only 147 subjects were 10 y or younger. The total number of exposed subjects was only 789 so that the probability of detecting a small risk was very low. Indeed, the risk estimate ( $RR = 0.9$ ) had a very

wide confidence interval (95% CI = 0.1–5.1). While there is little evidence to suggest that the use of diagnostic  $^{131}\text{I}$  in adults is carcinogenic, additional data are needed to clarify the risks associated with childhood medical exposure.

Little (2001, 2002) has compared risk coefficients in the atomic-bomb survivors to those from studies of patients receiving diagnostic radiation and concluded that the risks are smaller among the irradiated patients than the atomic-bomb survivors of similar age and sex and with comparable length of follow-up. He suggests that the difference may be due not only to the lower dose rate, but also to variation in background cancer rates in Japan compared with most of the Western countries where the patient studies were conducted. While radiation doses from most diagnostic examinations are low, because millions of people of all ages receive them, the collective dose is large. Of current concern is the health impact from the frequent and repeated use of relatively high-dose pediatric helical CT scans (Brenner et al. 2001; Donnelly et al. 2001; Slovis 2002).

### RADIATION TREATMENT FOR BENIGN DISEASES AND CONDITIONS

Radiation treatment for benign diseases was relatively common from the 1930's to the 1960's. While these treatments generally were effective, some resulted in enhanced cancer risks. As more was learned about radiation-associated cancer risks and new treatments became available, the use of radiotherapy for benign disease has declined. Radiation risk estimates have been reported for adult patients treated for ankylosing spondylitis, post-partum mastitis, benign gynecological disorders, benign lesions of the locomotor system, and peptic ulcer, and for children and adolescents treated for skin hemangiomas, tinea capitis, enlarged thymus gland, benign disease of the head and neck, including enlarged tonsils and acne (UNSCEAR 2000). Many of these cohorts have been followed for decades and they continue to yield new knowledge about partial body radiation, most often at moderate doses. The following section discusses selected recent follow-ups that help fill critical gaps in understanding radiation carcinogenesis.

Cancer mortality was updated in a cohort of peptic ulcer patients in Chicago with more than 50 y of follow-up (Carr et al. 2002). In this cohort of 1,831 patients treated with extremely high x-ray exposure to the stomach (mean dose 15 Gy) and the pancreas (mean dose 14 Gy), enhanced cancer mortality was observed more than 10 y after treatment when compared with 1,778 patients receiving other treatments. For the entire cohort, the  $\text{ERR}_{\text{Gy}}$  was 0.06 (95% CI = 0.02–0.10) for

stomach cancer and 0.04 (95% CI = 0–0.08) for cancer of the pancreas. When the analyses were restricted to patients receiving <10 Gy, the risks were larger ( $\text{ERR}_{\text{Gy}}$  = 0.20; 95% CI = 0–0.73 and  $\text{ERR}_{\text{Gy}}$  = 0.34; 95% CI = 0.09–0.89 for stomach and pancreatic cancer mortality, respectively). The very high background Japanese stomach cancer incidence and mortality rates compared with rates in most western populations make it questionable whether it is appropriate to extrapolate risk estimates from the atomic-bomb survivors directly to other populations. The peptic ulcer study adds to the sparse data on radiation-induced stomach cancer. The results indicate that at doses <10 Gy the mortality risk estimates are similar to those reported for the atomic-bomb survivors (Pierce et al. 1996).

Investigations of thyroid cancer subsequent to medical radiation, especially treatment for benign diseases, have yielded important quantitative information on low-dose effects, age at exposure, time since exposure, the influence of early detection screening on cancer incidence and radiation risk estimates, the clinical aspects of radiation-related tumors, and *RET* rearrangements (Schneider and Ron 2003). The large number of studies of childhood exposure all report statistically significant elevated thyroid cancer incidence and those with individual organ doses demonstrate a linear dose-response relationship with no evidence of a threshold (Table 4). In a pooled analysis of seven epidemiologic studies, the  $\text{ERR}_{\text{Gy}}$  for persons exposed before age 15 y was 7.7 (95% CI = 2.1–29). The results also indicate that risk continues throughout life and that there is a steep decline in risk with increasing age at exposure (Ron et al. 1995). In contrast, there is a paucity of data on risks associated with adult exposure. Among atomic-bomb survivors over age 20 at the time of the bombings there was no significant excess of thyroid cancer ( $\text{ERR}_{\text{sv}}$  = 0.1; 95% CI =  $\leq$ 0.23–0.75) (Thompson et al. 1994). Damber et al. (2001) recently reported a small but significantly elevated risk of thyroid cancer among 8,144 patients receiving radiotherapy to the cervical spine for benign lesions in the locomotor system. These patients received a mean dose to the thyroid gland of about 1 Gy resulting in an  $\text{ERR}_{\text{Gy}}$  of 0.58. No excess risk was observed among 19,271 patients who also had benign locomotor system conditions but who received radiation treatment in which the thyroid gland was not exposed. This study, along with studies of adult cancer patients showing small risks after high dose radiotherapy, suggest that there may be a small enhanced risk of thyroid cancer following adult radiation exposure, but it is much lower than that for childhood exposure.

In a new follow-up of the New York tinea capitis study (Shore et al. 2002), a significant increased risk of

**Table 4.** Thyroid cancer after childhood radiotherapy.<sup>a</sup>

Study	Reference	Mean dose	ERR <sub>Gy</sub>	EAR (10 <sup>4</sup> PY Gy) <sup>-1</sup>
Childhood cancer	Tucker et al. 1991	12	4.5 (3.1–6.4)	0.4 (0.2–0.5)
Tuberculosis, adenitis	Hanford et al. 1962	8.2	37 (16–72)	7.7 (3.3–15)
Chicago head and neck	DeGroot et al. 1983	4.5	12 (6.6–20)	3.5 (2.0–5.9)
Thymus adenitis	Maxon et al. 1980	2.9	4.5 (2.7–7.0)	1.2 (0.7–1.8)
Rochester enlarged thymus	Shore et al. 1993	1.4	9.5 (6.9–13)	3.0 (2.2–4.0)
Michael Reese enlarged tonsils	Schneider et al. 1993	0.6	3.0 (2.6–3.5)	38 (32–43)
Stockholm hemangioma	Lundell et al. 1994	0.3	4.9 (1.3–10)	0.9 (0.2–1.9)
Lymphoid hyperplasia	Pottern et al. 1990	0.2	5.9 (1.8–12)	9.1 (2.7–18)
Israel tinea capitis	Ron et al. 1989	0.1	34 (23–47)	13 (9.0–18)
New York tinea capitis	Shore 1992	0.1	7.7 (<0–60)	1.3 (<0–10)
Gotenburg hemangioma	Lindberg et al. 1995	0.1	7.5 (0.4–18)	1.6 (0.09–3.9)

<sup>a</sup> Adapted from Shore (1992) and UNSCEAR (2000).

basal cell carcinoma (ERR<sub>1Gy</sub> = 0.6, 95% CI 0.3–1.1), but not squamous cell carcinoma, was observed among white irradiated patients. In this cohort of 2,224 irradiated and 1,380 nonirradiated patients with tinea capitis, a constant relative risk was seen over time, and there appeared to be an interaction between the radiation exposure and exposure to ultraviolet (UV) radiation. Although the interaction could not be assessed directly, the increased risk of x-radiation-related skin cancer was higher in the head and neck areas not covered by hair than on the scalp and was not seen among black patients. It was notable that the risk decreased about 12% for each 1 y increase in age at exposure. The excess relative risks were very similar to those reported from the Israel tinea capitis study (ERR<sub>1Gy</sub> = 0.7, 95% CI 0.3–1.4) (Ron et al. 1991) and the atomic-bomb survivors (ERR<sub>1Gy</sub> = 0.6, 95% CI 0.3–1.1) (Ron et al. 1998a), even though the background rates of skin cancer differ substantially in the three populations. Among atomic-bomb survivors, the excess relative risks were similar for UV-exposed and UV-unexposed parts of the body.

Although the carcinogenic effects of moderate doses of therapeutic x and gamma radiation are fairly well described, much less is known about internally-deposited radionuclides. Since <sup>131</sup>I is the treatment of choice for hyperthyroidism, which is a rather common disease especially among women, more information is needed. Cohort studies of hyperthyroid patients have been conducted in Sweden (Holm et al. 1991; Hall et al. 1992), England (Franklyn et al. 1998, 1999), and the United States (Ron et al. 1998b). The treatment goal is to deliver radiation doses to the thyroid high enough to kill all the cells, thus there is a low probability of thyroid cancer induction. Yet, a small increased risk of thyroid cancer incidence or mortality has been observed in two out of the three cohorts (Franklyn et al. 1999; Ron et al. 1998b). Since the thyroid concentrates most of the radioiodine, doses to other organs are very small and the chance of

finding statistically significant radiation-related cancer risks in an epidemiologic study is limited. Ankylosing spondylitis patients treated with injected high-LET <sup>224</sup>Ra in Germany have an elevated risk of bone sarcomas (55 observed, 0.2 expected; mean bone dose = 31 Gy) and possibly cancers of the breast, liver, connective tissue, kidney, thyroid, and bladder (Henrichs et al. 1995; Spiess 1995; Nekolla et al. 1999, 2000). Only increased risks of leukemia (ERR<sub>1Gy</sub> = 2.4) were demonstrated in another study of German ankylosing spondylitis patients treated with much lower doses (mean bone dose ~6 Gy) of <sup>224</sup>Ra (Wick et al. 1995, 1999). In the first study, 24% of the patients were treated before age 20 y (Spiess 1995), whereas the patients in the second study were almost all treated as adults. Thus, the dissimilar age at exposure distribution in the two investigations might be another reason for the different results.

At moderate doses of x radiation, such as those most often used to treat benign diseases, excess cancer risks are observed in both children and adults in or near the radiation field. For example, following radiotherapy to the head and neck for benign conditions, excess cancers of the thyroid and salivary glands and central nervous system have been observed. Radiation-associated thyroid cancer, however, rarely occurs following adult exposure. Radiation therapy is again being used to treat benign conditions, e.g., to prevent restenosis after angioplasty, and to treat arteriovenous malformations and ocular macrodegeneration. Although few cancers are induced compared with the number of treated patients, the potential long-term sequelae of radiotherapy for benign disease should be considered when weighing risks and benefits of various available treatments.

## RADIOTHERAPY FOR CANCER

Second primary malignancies are a serious complication of high-dose radiotherapy for malignant diseases.

Significant improvement in cancer treatment over the last few decades has resulted in longer survival and a growing number of radiation-related second cancers. Radiotherapy-related second primary cancers can develop subsequent to most first primary cancers if survival is long enough, but risks of second malignancies have been particularly high following radiotherapy for childhood cancer. The types of second cancers seen following radiotherapy for a first cancer are usually the same as those observed in any irradiated population. However, because some organs and tissues are in the beam while others receive only scatter radiation, both high and low-dose effects can occur. Comprehensive reviews of secondary cancers and their association with treatment have been published in the last few years (Inskip 1999; van Leeuwen and Travis 2001; Bhatia and Sklar 2002). Thus, this short review will focus on recent studies with an emphasis on quantified risk estimates and dose response.

Second cancers following radiotherapy for childhood cancer, Hodgkin's disease, non-Hodgkin's lymphoma, and cancers of the breast, female genital tract, and testes have been studied in detail. The high risks observed following radiotherapy and the possibility of obtaining blood and/or tumor tissue make studies of cancer patients ideal for investigating interactions between radiation exposure and genetic susceptibility. One example of a proposed gene-environment interaction is observed among patients with retinoblastoma, a rare eye malignancy occurring in children. Radiation treatment for retinoblastoma is common and survival is good. Among hereditary retinoblastoma patients, the risk of developing a second cancer is high. In a cohort study of retinoblastoma patients, the 50 y cumulative incidence of a second malignancy was 58.3% ( $\pm$  8.9%) among patients treated with radiotherapy and 26.5% ( $\pm$  10.7%) among those not receiving radiotherapy. Among patients with nonhereditary retinoblastoma, the risk of second cancers was not increased measurably (Wong et al. 1997).

Second cancers are a leading cause of mortality in Hodgkin's disease survivors. Over 80% of patients with Hodgkin's disease are treated with radiotherapy, frequently with high doses to large fields. Children with Hodgkin's disease are of particular interest because the 5-y survival rate of childhood Hodgkin's disease is over 90% (Jemal et al. 2002), and the second cancer rate is relatively high. Among women who had Hodgkin's disease as children, a radiation-related excess of breast cancer has been observed in multiple studies (see review by Clemons et al. 2000), which was particularly notable among those receiving mantle field radiotherapy (Bhatia et al. 1996). Radiation-related secondary breast cancer

following childhood Hodgkin's disease tends to occur at a relatively early age (mean age 30–45 y) (Clemons et al. 2000). Among adult Hodgkin's disease survivors treated with radiation, breast cancer risk is slightly increased. This age at exposure effect is consistent with the pattern observed in the Life Span Study of atomic-bomb survivors (Thompson et al. 1994); however, as seen in Table 5, the magnitude of the excess risk per unit dose is lower in the cancer patients (Little 2002).

In the largest study of second cancers following Hodgkin's disease, increased risks of all second cancers were observed among radiation-treated patients, even after 25 y (Dores et al. 2002). Hodgkin's disease survivors receiving radiotherapy also had an enhanced risk of cancers of the esophagus, stomach, rectum, lung, breast, bladder, thyroid, bone and connective tissue, thyroid, non-Hodgkin's lymphoma and acute nonlymphocytic leukemia. The study, however, included patients of all ages and, therefore, some of the observed risks were due to the large risks in patients treated at a young age. Secondary lung cancer risk is the most common malignancy occurring after Hodgkin's disease (Travis et al. 2002). After adjusting for smoking and chemotherapy, secondary lung cancer appears to increase with increasing radiation dose to the irradiated location in the lung, even when doses reach more than 40 Gy. Among 222 lung cancer patients who had survived  $\geq$ 1 y, the lung cancer relative risk was 7.2 for patients receiving over 40 Gy (Travis et al. 2002).

Radiotherapy-associated second cancers among patients with testicular cancer also warrant attention, especially since many patients are diagnosed as young adults and the advances in treatment have led to marked improvement in survival and even complete cures. In an international study of 18,567 testicular cancer patients, with a mean age at diagnosis of 39 y, 36 patients developed leukemia within 17 y after treatment for their first cancer; 22 of these patients were treated with radiotherapy alone and another two received radiotherapy and alkylating agents. The authors reported a three-fold risk of secondary leukemia among patients receiving radiotherapy (mean active bone marrow dose 12.6 Gy) without chemotherapy. The risk of leukemia rose with increasing radiation dose, reaching 20-fold among patients treated with  $\geq$ 20 Gy (Travis et al. 2000).

Little (2002) estimated and then compared the  $ERR_{Sv}$  from studies of cancer patients and atomic-bomb survivors (Table 5). He found that the risks for cancer survivors were notably less than the for the atomic-bomb survivors of a similar age at exposure. The lower risk associated with high-dose radiotherapy is likely due to the effects of cell killing. Although the absolute number of radiation-related second cancers is small, they are a

Table 5. Secondary cancer risks following radiation therapy for a first malignancy.<sup>a</sup>

Secondary cancer site	Radiation treated first cancer	Study	Age at irradiation	Mean dose (range) Sv	Cancer patients ERR/Sv (95% CI)	LSS <sup>b</sup> ERR/Sv (95% CI)
Colon	Cervix	Boice et al. 1988	<30->75	24 (0->51)	-0.00 (-0.01-0.01)	0.75 (-0.05-2.18)
Pancreas	Cervix	Boice et al. 1988	<30->75	1.9 (0->3.4)	-0.02 (-0.17-0.35)	-0.35 (-0.58-0.12)
Lung	Hodgkin's disease	van Leeuwen and Travis 2001	<45->55	7.2 (0->21)	0.37 (0.01-1.16)	1.23 (0.43-2.45)
Bone	Childhood cancer	Tucker et al. 1987	<18	26.9 (0-159)	0.08 (0.03-0.18)	16.5 (2.6-157)
	Childhood cancer	Hawkins et al. 1996	<15	unk (0->75)	0.16 (0.07-0.37)	16.5 (2.6-157)
	Retinoblastoma	Wong et al. 1997	<17	33 (0-212)	0.19 (0.14-0.32)	16.5 (2.6-157)
Breast	Cervix	Boice et al. 1988	<30->75	22 (0->32)	0.01 (-0.02-0.11)	-0.27 (-0.34-0.21)
	Cervix	Boice et al. 1989	<30->75	0.31 (0-0.98)	0.63 (-0.56-2.66)	0.42 (-0.15-1.46)
	Hodgkin's disease	Hancock et al. 1993	4-81	unk (0-47)	0.03 (-0.08-0.87)	1.76 (0.94-2.92)
	Hodgkin's disease	Bhatia et al. 1996	1-16	30 (0-52)	0.36 (0.09-0.63)	2.07 (0.97-3.77)
	Contralateral breast	Boice et al. 1992	<45->55	2.8 (0-7.1)	0.07 (-0.02-0.18)	0.42 (-0.15-1.46)
	Contralateral breast	Storm et al. 1992	<45->55	2.5 (0->6)	-0.01 (-0.08-0.10)	0.42 (-0.15-1.46)
Uterus	Cervix	Boice et al. 1988	<30->75	165 (0->222)	0.00 (-0.00-0.02)	-36 (-0.92-0.21)
Ovary	Cervix	Boice et al. 1988	<30->75	32.1 (0->51)	0.01 (-0.00-0.06)	2.64 (0.42-7.20)
Kidney	Cervix	Boice et al. 1988	<30->75	2.0 (0->3.4)	0.30 (-0.10-1.63)	-0.32 (-1.36-0.72)
CNS	Childhood cancer	Little et al. 1998	0-17	6.2 (0-83)	0.19 (0.03-0.85)	0.96 (-1.08-4.41)
Thyroid	Childhood cancer	Tucker et al. 1991	<18	12.5 (0-76)	1.1 (0.4-29.4)	5.84 (2.64-12.1)
NHL	Cervix	Boice et al. 1988	<30->75	0.11 (0.01-0.24)	34.9 (-2.2->1000)	0.41 (-0.73-2.23)
Multiple myeloma	Cervix	Boice et al. 1988	<30->75	7.1 (0.5-25)	0.06 (-0.03-0.46)	-0.23 (-0.96-0.50)
Leukemia	Cervix	Boice et al. 1988	<30->75	7.1 (0.5-25)	0.01 (-0.05-0.27)	-0.23 (-1.02-0.55)
	Cervix	Boice et al. 1987	<30->75	7.1 (0.5-25)	0.03 (-0.06-0.12)	5.17 (1.99-11.9)
	Childhood cancer	Tucker et al. 1987	<18	10 (0-38)	-0.00 (-0.03-0.09)	16.1 (7.22-37.6)
	Hodgkin's disease	Kaldor et al. 1990	42	unk (0->20)	0.24 (0.04-0.43)	5.24 (3.58-7.55)
	Hodgkin's disease	Boivin et al. 1995	<15->35	unk (0->30)	0.01 (0.00-0.02)	5.24 (3.58-7.55)
	Testicular	Travis et al., 1995	<30->50	13.6 (7.9-24)	0.27 (0.02-1.2)	3.34 (1.57-6.36)
	Breast	Curtis et al. 1992	<50->70	7.5 (0->11)	1.53 (-18.2-21.2)	8.2 (1.86-33.5)

<sup>a</sup> Adapted from Little (2002).<sup>b</sup> Life Span Study.

grave late effect of radiotherapy. As information about second cancers increases, medical practitioners are becoming more aware of the potential long-term consequences of high dose radiotherapy. As a result, additional effort is now made to minimize exposure to nontumor tissue and organs whenever possible. In current practice, radiotherapy doses have been reduced for Hodgkin's disease, testicular cancer, and breast cancer. Consequently, the incidence of treatment-related second cancers may decrease in the future.

## CONCLUSION

As a body of literature, the numerous epidemiologic studies of medical radiation have been remarkably informative and have provided a needed complement to the studies of the atomic-bomb survivors. In general, the results have been consistent with the findings from the atomic-bomb survivors, e.g., young age at exposure appears to enhance the risk of radiation-related tumors of many sites and radiation-related risks appear to persist throughout life. On the other hand, the medical studies suggest that fractionation can diminish the excess risk for some cancer sites such as lung cancer and that extremely high radiation doses (on the order of tens of gray) lower risk, probably because of cell killing. A twofold higher excess relative risk of all sites cancer incidence for women compared with men was observed in the atomic-bomb survivors. A comparable comprehensive evaluation of gender differences in medically irradiated populations has not been conducted. This issue deserves more attention.

Since the use of radiation in medicine is widespread and appears to be increasing in the United States, there is a compelling need for additional data to quantify the long-term health effects of the diagnostic and therapeutic uses of radiation. Continued follow-up of existing cohorts will be valuable to assess lifetime risks. The establishment of cohorts of patients exposed to new or modified diagnostic and treatment protocols may help resolve questions in these emerging areas.

## REFERENCES

- Bhatia S, Sklar C. Second cancers in survivors of childhood cancer. *Nature Rev* 2:124-132; 2002.
- Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, Meadows AT. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med* 334:745-751; 1996.
- Boice JD Jr, Blettner M, Kleinerman RA, Stovall M, Moloney WC, Engholm G, Austin DF, Bosch A, Cookfair DL, Kremenz ET, et al. Radiation dose and leukemia risk in patients treated for cancer of the cervix. *J Natl Cancer Inst* 79:1295-1311; 1987.
- Boice JD Jr, Engholm G, Kleinerman RA, Blettner M, Stovall M, Lisco H, Moloney WC, Austin DF, Bosch A, Cookfair DL, Kremenz ET, Latourette HB, Merrill JA, Peters LJ, Schultz MD, Storm HH, Bjorkholm E, Pettersson F, Bell CMJ, Coleman MP, Fraser P, Neal FE, Prior P, Choi NW, Hislop TG, Koch M, Kreiger N, Robb D, Robson D, Thompson DH, Lochmuller H, von Fournier D, Frischkorn R, Khorstad KE, Rimpela A, Pejovic M-H, Pompe Kim V, Stankusova H, Berrino F, Sigurdsson K, Hutchison GB, MacMahon B. Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res* 116:3-55; 1988.
- Boice JD Jr, Blettner M, Kleinerman RA, Engholm G, Stovall M, Lisco H, Austin DF, Bosch A, Harlan L, Kremenz ET, et al. Radiation dose and breast cancer risk in patients treated for cancer of the cervix. *Int J Cancer* 44:7-16; 1989.
- Boice JD Jr, Preston DL, Davis FG, Monson RR. Frequent chest x-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. *Radiat Res* 125:214-222; 1991a.
- Boice JD Jr, Morin MM, Glass AG, Friedman GD, Stovall M, Hoover RN, Fraumeni JF Jr. Diagnostic x-ray procedures and risk of leukemia, lymphoma and multiple myeloma. *J Am Med Assoc* 265:1290-1294; 1991b.
- Boice JD Jr, Harvey EB, Blettner M, Stovall M, Flannery JT. Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med* 326:781-785; 1992.
- Boice JD Jr, Miller RW. Childhood and adult cancer after intrauterine exposure to ionizing radiation. *Teratology* 59:227-233; 1999.
- Boivin JF, Hutchison GB, Zauber AG, Bernstein L, Davis FG, Michel RP, Zanke B, Tan CT, Fuller LM, Mauch P, et al. Incidence of second cancers in patients treated for Hodgkin's disease. *J Natl Cancer Inst* 87:732-741; 1995.
- Brenner DJ, Elliston CD, Hall EJ, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. *Am J Roentgenol* 176:289-296; 2001.
- Carr ZA, Kleinerman RA, Stovall M, Weinstock RM, Griem ML, Land CE. Malignant neoplasms after radiation therapy for peptic ulcer. *Radiat Res* 157:668-677; 2002.
- Clemons M, Loijens L, Goss O. Breast cancer risk following irradiation for Hodgkin's disease. *Cancer Treat Rev* 26:291-302; 2000.
- Curtis RE, Boice JD Jr, Stovall M, Bernstein L, Greenburg RS, Flannery JT, Schwartz AG, Weyer P, Moloney WC, Hoover RN. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. *N Engl J Med* 326:1745-1751; 1992.
- Damber L, Johansson L, Johansson R, Larsson LG. Thyroid cancer after x-ray treatment of benign disorders of the cervical spine in adults. *Acta Oncologica* 41:25-28; 2001.
- Davis FG, Boice JD Jr, Hrubec Z, Monson RR. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. *Cancer Res* 49:6130-6136; 1989.
- DeGroot L, Reilly M, Pinnameneni K, Refetoff S. Retrospective and prospective study of radiation-induced thyroid disease. *Am J Med* 74:852-862; 1983.
- Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol* 70:130-139; 1997.
- Donnelly LF, Emery KH, Brody AS, Laor T, Gylys-Morin VM, Anton CG, Thomas SR, Frush DP. Minimizing radiation dose for pediatric body applications of single-detector helical CT: strategies at a large Children's Hospital. *Am J Roentgenol* 176:303-306; 2001.
- Doody MM, Lonstein JE, Stovall M, Hacker DG, Luckyanov N, Land CE. Breast cancer mortality following diagnostic

x-rays: findings from the U. S. Scoliosis Cohort Study. *Spine* 25:2052-2063; 2000.

- Dores G, Metayer C, Curtis RE, Lynch CF, Clarke EA, Glimelius B, Storm H, Pukkala E, van Leeuwen FE, Holowaty EJ, Andersson M, Wiklund T, Joensuu T, vant Veer MB, Stovall M, Gospodarowicz M, Travis LB. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation of 32,591 patients over 25 years. *J Clin Oncol* 20:3484-3494; 2002.
- dos Santos Silva I, Jones M, Malveiro F, Swerdlow A. Mortality in the Portuguese Thorotrast study. *Radiat Res* 152:S88-S92; 1999.
- Franklyn JA, Maisonneuve P, Sheppard MC, Betteridge J, Boyle P. Mortality after the treatment of hyperthyroidism with radioactive iodine. *N Engl J Med* 338:712-718; 1998.
- Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J, Boyle P. Cancer incidence and mortality after radiologic treatment for hyperthyroidism: a population-based cohort study. *Lancet* 353:2111-2115; 1999.
- Hahn K, Schnell-Inderst P, Grosche B, Holm LE. Thyroid cancer after diagnostic administration of iodine-131 in childhood. *Radiat Res* 156:61-70; 2001.
- Hall EJ. *Radiobiology for the radiologist*. Philadelphia: Lippincott Williams & Wilkins; 2000.
- Hall P, Berg G, Bjelkengren G, Boice JD Jr, Ericsson UB, Hallquist A, Lidberg M, Lundell G, Tennvall J, Wiklund K, Holm L-E. Cancer mortality after iodine-131 therapy for hyperthyroidism. *Int J Cancer* 50:886-890; 1992.
- Hall P, Mattsson A, Boice JD Jr. Thyroid cancer after diagnostic administration of iodine-131. *Radiat Res* 145:86-92; 1996.
- Hallquist A, Nasman A. Medical diagnostic x-ray radiation—an evaluation from medical records and dentist cards in a case-control study of thyroid cancer in the northern medical region of Sweden. *Eur J Cancer Prev* 10:147-152; 2001.
- Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst* 85:25-31; 1993.
- Hanford JM, Quimby E, Frantz V. Cancer arising many years after radiation therapy. *J Am Med Assoc* 181:132-138; 1962.
- Hawkins MM, Wilson LMK, Burton HS, Potok MHN, Winter DL, Marsden HB, Stovall MA. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Nat Cancer Inst* 88:270-278; 1996.
- Henrichs KL, Bogner L, Nekolla E, Nosske D, Roedler-Vogelsang T. Extended dosimetry for studies with Ra-224 patients. In: van Kaick G, Karaoglou A, Kellerer AM, eds. *Health effects of internally deposited radionuclides: emphasis on radium and thorium*. Singapore: World Scientific; 1995: 33-38.
- Holm LE, Wiklund KE, Lundell GE, Bergman NA, Bjelkengren G, Ericsson UB, Cederquist ES, Lidberg ME, Lindberg RS, Wicklung HV, et al. Cancer risk in population examined with diagnostic doses of <sup>131</sup>I. *J Natl Cancer Inst* 81:302-306; 1989.
- Holm LE, Hall P, Wiklund K, Lundell G, Berg G, Bjelkengren G, Cederquist E, Ericsson UB, Hallquist A, Larsson L-G, Lidberg M, Lindberg S, Tennvall J, Wiklund H, Boice JD Jr. Cancer risk after iodine-131 therapy for hyperthyroidism. *J Natl Cancer Inst* 83:1072-1077; 1991.
- Howe GR. Lung cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with lung cancer mortality in the atomic bomb survivors study. *Radiat Res* 142:295-305; 1995.
- Howe GR, McLaughlin J. Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic-bomb survivors study. *Radiat Res* 145:694-707; 1996.
- Infante-Rivard C, Jacques L. Empirical study of parental recall bias. *Am J Epidemiol* 152:480-486; 2000.
- Infante-Rivard C, Mathonnet G, Sinnett D. Risk of childhood leukemia associated with diagnostic irradiation and polymorphisms in DNA repair genes. *Environ Health Perspect* 108:495-498; 2000.
- Inskip PD. Second cancers following radiotherapy. In: Neugut AI, Meadows AT, Robinson E, eds. *Multiple primary cancers*. Philadelphia PA: Lippincott Williams & Wilkins; 1999: 91-135.
- Inskip PD, Ekbohm A, Galanti MR, Grimelius L, Boice JD Jr. Medical diagnostic x rays and thyroid cancer. *J Natl Cancer Inst* 87:1613-1621; 1995.
- Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin* 52:23-47; 2002.
- Kaldor JM, Day NE, Clarke EA, van Leeuwen FE, Henry-Amar M, Fiorentino MV, Bell J, Pedersen D, Band P, Assouline D, et al. Leukemia following Hodgkin's disease. *N Engl J Med* 322:7-13; 1990.
- Knox EH, Stewart AM, Kneale GW, Gilman EA. Prenatal irradiation and childhood cancer. *J Soc Radiol Prot* 7:177-189; 1987.
- Lindberg S, Karlsson P, Arvidsson B, Holmberg E, Lunberg LM, Wallgren A. Cancer incidence after radiotherapy for skin hemangioma during infancy. *Acta Oncol* 34:735-740; 1995.
- Little MP. Cancer after exposure to radiation in the course of treatment for benign and malignant disease. *Lancet Oncol* 2:212-220; 2001.
- Little MP. Comparison of the risks of cancer incidence and mortality following radiation therapy for benign and malignant disease with the cancer risks observed in the Japanese a-bomb survivors. *Int J Radiat Biol* 78:145-163; 2002.
- Little MP, Boice JD Jr. Comparison of breast cancer incidence in the Massachusetts fluoroscopy cohort and in the Japanese atomic bomb survivors. *Radiat Res* 151:218-224; 1999.
- Little MP, de Vathaire F, Shamsaldin A, Oberlin O, Campbell S, Grimaud E, Chavaudra J, Haylock RG, Muirhead CR. Risks of brain tumour following treatment for cancer in childhood: modification by genetic factors, radiotherapy and chemotherapy. *Int J Cancer* 78:269-275; 1998.
- Lundell M, Hakulinen T, Holm L-E. Thyroid cancer after radiotherapy for skin hemangioma in infancy. *Radiat Res* 140:334-339; 1994.
- Maxon HR, Saenger EL, Thomas SR, Buncher CR, Kereiakes JG, Shafer ML, McLaughlin CA. Clinically important radiation-associated thyroid disease. A controlled study. *J Am Med Assoc* 244:1802-1805; 1980.
- Meinert R, Kaletsch U, Kaatsch P, Schuz J, Michaelis J. Associations between childhood cancer and ionizing radiation: results of a population-based case-control study in Germany. *Cancer Epidemiol Biomarkers Prev* 8:793-799; 1999.
- Mettler FA Jr, Briggs JE, Carchman R, Altobelli KK, Hart BL, Kelsey CA. Use of radiology in U.S. general short-term hospitals: 1980-1990. *Radiol* 189:377-380; 1993.

- Mori T, Kido C, Fukutomi K, Kato Y, Hatakeyama S, Machinami R, Ishikawa Y, Kumatori T, Sasaki F, Hiroto Y, Kiyosawa K, Hayashi S, Tanooka H, Sobue T. Summary of entire Japanese Thorotrast follow-up study: updated 1998. *Radiat Res* 152:S84-S87; 1999.
- Naumburg E, Bellocco R, Cnattingius S, Hall P, Boice JD Jr, Ekbohm A. Intrauterine exposure to diagnostic x rays and risk of childhood leukemia subtypes. *Radiat Res* 156:718-725; 2001.
- Nekolla E, Kellerer AM, Kuse-Isingschulte M, Eder E, Spiess H. Malignancies in patients treated with high doses of radium-224. *Radiat Res* 152:S3-S7; 1999.
- Nekolla EA, Kreisheimer M, Kellerer AM, Kuse-Isingschulte M, Gossner W, Spiess H. Induction of malignant bone tumours in radium-224 patients: risk estimates based on the improved dosimetry. *Radiat Res* 153:93-103; 2000.
- Nyberg U, Nilsson B, Travis LB, Holm L-E, Hall P. Cancer incidence among Sweden patients exposed to radioactive Thorotrast: a forty-year follow-up survey. *Radiat Res* 157:419-425; 2002.
- Pierce DA, Shimizu Y, Preston DL, Vaeth M, Mabuchi K. Studies of the mortality of A-bomb survivors. Report 12, Part 1. Cancer: 1950-1990. *Radiat Res* 146:1-27; 1996.
- Platz EA, Wiencke JK, Kelsy KT, Janower ML, Schottenfeld D, Travis L, Goldman MB. Chromosomal aberrations and HPRT mutant frequencies in long-term American Thorotrast survivors. *Int J Radiat Biol* 76:955-961; 2000.
- Pottern LM, Kaplan M, Larsen P, Silva JE, Koenig RJ, Lubin JH, Stovall M, Boice JD Jr. Thyroid nodularity after childhood irradiation for lymphoid hyperplasia: a comparison of questionnaire and clinical findings. *J Clin Epidemiol* 43:449-460; 1990.
- Preston-Martin S, Bernstein L, Maldonado AA, Henderson BE, White SC. A dental x-ray validation study. *Am J Epidemiol* 121:430-439; 1985.
- Preston-Martin S, Thomas DC, White SC, Cohen D. Prior exposure to medical and dental x-ray related to tumors of the parotid gland. *J Natl Cancer Inst* 80:943-949; 1988.
- Preston-Martin S, Thomas DC, Yu MC, Henderson BE. Diagnostic radiography as a risk factor for chronic myeloid and monocytic leukaemia (CML). *Br J Cancer* 59:639-644; 1989.
- Ron E, Modan B, Preston DL, Alfandary E, Stovall M, Boice JD Jr. Thyroid neoplasia following low-dose radiation in childhood. *Radiat Res* 120:516-531; 1989.
- Ron E, Modan B, Preston D, Alfandary E, Stovall M, Boice JD Jr. Radiation-induced skin carcinomas of the head and neck. *Radiat Res* 125:318-325; 1991.
- Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice JD Jr. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 141:259-277; 1995.
- Ron E, Preston DL, Kishikawa M, Kobue T, Iseki M, Tokunaga S, Tokunaga M, Mabuchi K. Skin tumor risk among atomic bomb survivors. *Cancer Causes Control* 9:393-401; 1998a.
- Ron E, Doody MM, Becker D, Brill AB, Curtis RE, Goldman MB, Harris B, Hoffman DA, Maxon H, McConahey W, Preston-Martin S, Warshauer E, Wong FL, Boice JD Jr. Cancer mortality following treatment for hyperthyroidism. *JAMA* 280:347-355; 1998b.
- Schneider AB, Ron E. Radiation and thyroid cancer: lessons from a half century of study. In: Braverman LE, ed. *Diseases of the thyroid*. Totowa, NJ: Humana Press; 2003.
- Schneider AB, Ron E, Lubin J, Stovall M, Gierlowski TC. Dose-response relationships for radiation-induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on the thyroid. *J Clin Endocrinol Metab* 77:362-364; 1993.
- Sherman GJ, Howe GR, Miller AB, Rosenstein M. Organ dose per unit exposure resulting from fluoroscopy for artificial pneumothorax. *Health Phys* 35:259-269; 1978.
- Shore RE. Issues and epidemiological evidence regarding radiation-induced thyroid cancer. *Radiat Res* 131:98-111; 1992.
- Shore RE, Hildreth N, Dvoretzky P, Andresen E, Moseson M, Pasternack B. Thyroid cancer among persons given x-ray treatment in infancy for an enlarged thymus gland. *Am J Epidemiol* 137:1068-1080; 1993.
- Shore RE, Moseson M, Xue X, Tse Y, Harley N, Pasternack BS. Skin cancer after x-ray treatment for scalp ringworm. *Radiat Res* 157:410-418; 2002.
- Shu XO, Jin F, Linet MS, Zheng W, Clemens J, Mills J, Gao YT. Diagnostic x-ray and ultrasound exposure and risk of childhood cancer. *Br J Cancer* 70:531-536; 1994.
- Shu XO, Potter JD, Linet MS, Severson RK, Han D, Kersey JH, Neglia JP, Trigg ME, Robison LL. Diagnostic x-rays and ultrasound exposure and risk of childhood acute lymphoblastic leukemia by immunophenotype. *Cancer Epidemiol Biomarkers Prev* 11:177-185; 2002.
- Slovits TL, ed. Conference on the ALARA (as low as reasonably achievable) concept in pediatric CT intelligent dose reduction. *Pediatr Radiol* 32:217-317; 2002.
- Spiess H. The Ra-224 study: past, present and future. In: van Kaick G, Karaoglou A, Kellerer AM, eds. *Health effects of internally deposited radionuclides: emphasis on radium and thorium*. Singapore: World Scientific; 1995: 157-163.
- Stewart A, Webb J, Giles D, Hewitt D. Malignant disease in childhood and diagnostic irradiation in utero. *Lancet* 2:447; 1956.
- Storm HH, Andersson M, Boice JD Jr, Blettner M, Stovall M, Mouridsen HT, Dombrowsky P, Rose C, Jacobsen A, Pedersen M. Adjuvant radiotherapy and risk of contralateral breast cancer. *J Natl Cancer Inst* 84:1245-1250; 1992.
- Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochiaiubo S, Sugimoto S, Ikeda T, Terasaki M, Izumi S, et al. Cancer incidence in atomic bomb survivors. Part II. Solid tumours, 1958-87. *Radiat Res* 137:S17-S67; 1994.
- Travis LB, Curtis RE, Hankey BF. Second malignancies after testicular cancer. *J Clin Oncol* 13:533-534; 1995.
- Travis LB, Andersson M, Gospodarowicz M, van Leeuwen FE, Bergfeldt K, Lynch CF, Curtis RE, Kohler BA, Wiklund T, Storm H, Holowaty E, Hall P, Pukkala E, Sleijfer DT, Clarke EA, Boice JD Jr, Stovall M, Gilbert E. Treatment-associated leukemia following testicular cancer. *J Natl Cancer Inst* 92:1165-1171; 2000.
- Travis LB, Land CE, Andersson M, Byberg U, Goldman MB, Gaul LK, Berger E, Storm HH, Hall P, Auvinen A, Janower ML, Holm LE, Monson RR, Schottenfeld D, Boice JD Jr. Mortality after cerebral angiography with or without radioactive Thorotrast: an international cohort of 3,143 two-year survivors. *Radiat Res* 156:136-150; 2001.
- Travis LB, Gospodarowicz M, Curtis RE, Clarke EA, Anderson M, Glimelius B, Joensuu T, Lynch CF, van Leeuwen FE, Holowaty E, Storm H, Glimelius I, Pukkala E, Stovall M, Fraumeni JF Jr, Boice JD Jr, Gilbert E. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst* 94:182-192; 2002.
- Tucker MA, Meadows AT, Boice JD Jr, Stovall M, Oberlin O, Stone BJ, Birch J, Voute PA, Hoover RN, Fraumeni JF Jr. Leukemia after therapy with alkylating agents for childhood cancer. *J Natl Cancer Inst* 78:459-464; 1987.

- Tucker MA, Morris Jones PH, Boice JD Jr, Robison LL, Stone BJ, Stovall M, Jenkin RD, Lubin JH, Baum ES, Siegel SE, et al. Therapeutic radiation at a young age is linked to secondary thyroid cancer. *Cancer Res* 51:2885-2888; 1991.
- United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of atomic radiation. Ionizing radiation. New York: United Nations; Sales publication E.94.IX.11; 1994.
- United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and effects of atomic radiation. Ionizing radiation. New York: United Nations; Sales publication E.00. IX4; 2000.
- van Kaick G, Dalheimer A, Hornik S, Kaul A, Liebermann D, Luhrs H, Spiethoff A, Wegener K, Wesch H. The German Thorotrast study: recent results and assessment of risks. *Radiat Res* 152:S64-S71; 1999.
- van Leeuwen FE, Travis LB. Second cancers. In: Devita VT, Hellman S, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. Philadelphia: Lippincott Williams & Wilkins; 2001: 2939-2964.
- Wick RR, Chmelevsky D, Gossner W. Current status of the follow-up of radium-224 treated ankylosing spondylitis patients. In: van Kaick G, Karaoglou A, Kellerer AM, eds. *Health effects of internally deposited radionuclides: emphasis on radium and thorium*. Singapore: World Scientific; 1995: 165-169.
- Wick RR, Nekolla EA, Gossner W, Kellerer AM. Late effects in ankylosing spondylitis patients treated with 224Ra. *Radiat Res* 152:S8-S11; 1999.
- Wong FL, Boice JD Jr, Abramson DH, Tarone RE, Kleinerman RA, Stovall M, Goldman MB, Seddon JM, Tarbell N, Fraumeni JF Jr, Li FP. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *J Am Med Assoc* 278:1262-1267; 1997.

