Cancer Risks Associated With External Radiation From Diagnostic Imaging Procedures

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The 600% increase in medical radiation exposure to the US population since 1980 has provided immense benefit, but increased potential future cancer risks to patients. Most of the increase is from diagnostic radiologic procedures. The objectives of this review are to summarize epidemiologic data on cancer risks associated with diagnostic procedures, describe how exposures from recent diagnostic procedures relate to radiation levels linked with cancer occurrence, and propose a framework of strategies to reduce radiation from diagnostic imaging in patients. We briefly review radiation dose definitions, mechanisms of radiation carcinogenesis, key epidemiologic studies of medical and other radiation sources and cancer risks, and dose trends from diagnostic procedures. We describe cancer risks from experimental studies, future projected risks from current imaging procedures, and the potential for higher risks in genetically susceptible populations. To reduce future projected cancers from diagnostic procedures, we advocate the widespread use of evidence-based appropriateness criteria for decisions about imaging procedures; oversight of equipment to deliver reliably the minimum radiation required to attain clinical objectives; development of electronic lifetime records of imaging procedures for patients and their physicians; and commitment by medical training programs, professional societies, and radiation protection organizations to educate all stakeholders in reducing radiation from diagnostic procedures. CA Cancer J Clin 2012;62:75-100. Published 2012 American Cancer Society.†

Introduction

Since the discoveries of x-rays, radium, and radioactivity from uranium salts during the late 19th century, remarkable experimental, clinical, and technological developments in radiologic imaging have continued to transform medicine, as summarized in Table 1.1,2 A few years after x-rays were first used for radiologic imaging, physicians and other medical radiation workers developed skin carcinomas, leukemia, dermatitis, cataracts, and other adverse health effects.7-10 Despite early recommendations to decrease stray radiation to the patient and restrict the x-ray beam,8,11 25 years passed before these recommendations were implemented1 and radiation protection committees were established.12 With the development and evolution of measures of radiation dose, film badge monitoring, and personal (eg, lead aprons) and general (eg, lead shields) radiation protection equipment,2 occupational doses declined dramatically3,13,14 and the excesses of leukemia, skin cancer, and female breast cancer in medical radiation workers employed before 1950 were no longer apparent in subsequent medical radiation workers.3

From 1956 to the present, epidemiologic studies have also linked diagnostic x-rays with cancer increases in patients, including modest excesses of pediatric leukemia in the offspring of mothers undergoing diagnostic x-rays during pregnancy,15-19 and increased breast cancer risks in women with tuberculosis who were monitored using fluoroscopy20-23 and in women with scoliosis who were evaluated with repeated x-rays.24 During the past 30 years, newer imaging modalities (such as computed tomography [CT], myocardial perfusion scans, positron emission tomography [PET], and other radiologic procedures) dramatically increased. These procedures have provided immense clinical benefit but also higher ionizing radiation exposures to patients. Medical radiation now comprises almost 50% of the per capita radiation dose, compared with 15% in the early 1980s (Fig. 1).25 Although the individual risk of developing radiation-related cancer from any single medical imaging procedure is extremely small, the substantial increase in the per capita effective dose between 1980 and 2006, as well as reports of a substantial fraction of patients undergoing repeated higher dose examinations, motivate this review.25,26

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We are grateful to Annelie Landgren, MPH, and Stephanie Glagola, BA, for technical support.

DISCLOSURES: This review was supported by the Intramural Research Program of the National Institutes of Health and the National Cancer Institute.

Published 2012 American Cancer Society, Inc. †This article is a US Government work and, as such, is in the public domain in the United States of America. doi:10.3322/caac.21132. Available online at http://cacancerjournal.com
The objectives of this review are to summarize the key epidemiologic and experimental data on cancer risks associated with diagnostic radiologic procedures, to relate radiation exposures from recent and current imaging procedures to radiation levels statistically associated with cancer risks, and to propose a framework of strategies for reducing future cancer risks projected from current levels of diagnostic imaging procedures in patients.

### TABLE 1. Key Discoveries and Technological Developments in Diagnostic Radiography

<table>
<thead>
<tr>
<th>YEAR</th>
<th>DISCOVERIES AND TECHNOLOGICAL DEVELOPMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1895</td>
<td>Roentgen: x-rays</td>
</tr>
<tr>
<td>1896</td>
<td>Edison: calcium tungstate</td>
</tr>
<tr>
<td>1904</td>
<td>Self-regulated gas tubes</td>
</tr>
<tr>
<td>1908</td>
<td>Snook: generator provides selectable kV and mA</td>
</tr>
<tr>
<td>1913</td>
<td>Coolidge: first successful roentgen-ray tube</td>
</tr>
<tr>
<td>1914-1916</td>
<td>Patterson: fluoroscopic screen</td>
</tr>
<tr>
<td>1917</td>
<td>Potter-Bucky diaphragm: reduce scatter by secondary radiation</td>
</tr>
<tr>
<td>1924</td>
<td>Film changer for serial x-rays</td>
</tr>
<tr>
<td>1928</td>
<td>Siemens: 3-phase generators</td>
</tr>
<tr>
<td>1929</td>
<td>Hans Bouwers (at Philips research laboratories): rotating anode x-ray tube, shielding provided by tube housing integrated in tube assembly</td>
</tr>
<tr>
<td>1934</td>
<td>Ziedes des Plantes: optical subtraction of radiographic film to aid in visualization of small blood vessels</td>
</tr>
<tr>
<td>1941</td>
<td>First automatic film processor</td>
</tr>
<tr>
<td>1942</td>
<td>X-ray phototimers</td>
</tr>
<tr>
<td>1947</td>
<td>Xeroradiography</td>
</tr>
<tr>
<td>1948</td>
<td>Colman: image intensifier tube for fluoroscopy</td>
</tr>
<tr>
<td>1960</td>
<td>DuPont: polyester film base replaces acetate</td>
</tr>
<tr>
<td>1964</td>
<td>Kodak: 90-s Xomat processor</td>
</tr>
<tr>
<td>1964-1968</td>
<td>Cormack and Hounsfield: CT scanner</td>
</tr>
<tr>
<td>1969</td>
<td>Dedicated mammographic unit with molybdenum target tube and compression cone</td>
</tr>
<tr>
<td>1971</td>
<td>Xeroradiography system for mammography</td>
</tr>
<tr>
<td>1972</td>
<td>Screen film system for mammography</td>
</tr>
<tr>
<td>1973</td>
<td>Buchanan: rare earth screen phosphors</td>
</tr>
<tr>
<td>1979</td>
<td>Fuji Photo Film Co.: digital subtraction angiography</td>
</tr>
<tr>
<td>1982</td>
<td>Ultrafast CT scanner</td>
</tr>
<tr>
<td>1984</td>
<td>Computed radiography systems</td>
</tr>
<tr>
<td>1985</td>
<td>American College of Radiology–National Electrical Manufacturers Association Digital Imaging and Communication Standard to develop standards for medical picture archiving and communications (PACS)</td>
</tr>
<tr>
<td>1989</td>
<td>Heiken et al: slip-ring helical CT volume imaging</td>
</tr>
<tr>
<td>1993</td>
<td>Solid state digital x-ray detectors</td>
</tr>
<tr>
<td>1999</td>
<td>4-slice CT system</td>
</tr>
<tr>
<td>2000</td>
<td>Digital mammography system</td>
</tr>
<tr>
<td>2001</td>
<td>16-slice CT system with submillimeter collimation</td>
</tr>
<tr>
<td>2004</td>
<td>64-slice CT system</td>
</tr>
</tbody>
</table>

kV indicates kilovolts; mA, milliamperes; CT, computed tomography; PACS, picture archiving and communication system.

Background

Radiation Dose Measures

The radiation dose is the amount of energy absorbed in the body from radiation interactions. Early nonquantitative measures of dose, based on skin erythema, were replaced by measures of exposure (eg, the ability of x-rays to ionize air, measured in roentgens [or R]) and measures of absorbed dose (eg, energy absorption, measured initially in radiation absorbed dose [or rad] and more recently in gray [Gy] or milligray [mGy] [1 Gy = 100 rad; 1 rad = 10 mGy or 0.01 Gy]). Shown in Table 2 are definitions of the key dose quantities and units. Different types of radiation may produce different biological effects and the magnitude of the effect can vary according to the rate at which radiation is received (dose rate). The dose rate is a primary factor in determining the biological effects of a given absorbed dose. For example, as the dose rate is reduced and the exposure time extended, the biologic effect of a given dose is generally reduced. Relative biological effectiveness, which denotes the ability of a given type of radiation to produce a specific biological outcome compared with x-rays or gamma rays, is taken into account by the sievert (Sv), a metric for biological equivalent dose that can be used to measure mixed types of radiation exposure. The effective dose is the sum of the equivalent doses to each tissue and organ exposed multiplied by the appropriate tissue-weighting factor or, in other words, the whole-body dose of x-rays that would have to be delivered to produce the same carcinogenic risk as the partial dose that was delivered. This quantity provides an easy assessment of overall risk and makes the comparison of risks much simpler. Although effective dose is emphasized in many surveys because this metric is related to the risk of carcinogenic effects, effective dose cannot be measured and cannot be used for individual risk assessment. Only absorbed dose to a given tissue or organ can be used for estimating cancer risks.

Biological Mechanisms of Radiation Carcinogenesis

Ionizing radiation is an established carcinogen, based on animal studies and studies of early radiologists, radium dial workers (who used radium-containing paint for glow-in-the-dark...
Radiation-induced dermatitis, which was initially described in 1902, is a long-recognized adverse deterministic effect. Deterministic effects occur above a threshold dose and are characterized by a dose-related increasing risk and associated severity of outcome in the absence of adequate repair. Deterministic effects occur above a threshold dose and are characterized by a dose-related increasing risk and associated severity of outcome in the absence of adequate repair. A long-recognized adverse deterministic effect is radiation-induced dermatitis, which was initially described in 1902. After radiotherapy or fluoroscopically guided interventional procedures, generalized erythema may occur within hours and then fade within hours to days, followed by a second phase of sustained erythema manifesting 10 to 14 days after the exposure. The early erythema is considered to be an acute inflammatory reaction with an increase in vascular permeability, while the more sustained erythema, without other epidermal changes, is thought to be mediated by cytokines. Radiation cataractogenesis, particularly the occurrence of posterior subcapsular opacities, has been considered to be another classic example of a deterministic late effect. Formerly, the threshold was reported to be 2 Gy for acute radiation exposure, 4 Gy for fractionated doses, and even higher levels for long-term exposure, but recent human and mechanistic studies suggest a lower (eg, around 0.5 Gy) or no threshold.

Stochastic effects, including cancer and hereditary effects, are caused by a mutation or other permanent change in which the cell remains viable. The probability of a stochastic effect increases with dose (probably with no threshold, an assumption based on molecular knowledge of carcinogenesis: a very small x-ray dose can cause a base change in DNA), but the severity of the outcome is not related to the dose. For many years, radiation dose-related cancer risks at low doses were generally estimated from results of the follow-up studies of the atomic bomb survivors and of patients treated with moderate- to high-dose radiation. Major national and international radiation expert committees concluded in comprehensive reviews published during 2005 to 2008 that the available biological and biophysical data support a linear no-threshold risk model for cancer (eg, dose response at low levels occurs in a generally linear pattern without evidence of a threshold), and that this combined with an uncertain dose and dose rate effectiveness factor for extrapolation from high doses continues to be considered a conservative basis for radiation protection at low doses and dose rates. Some recent

<table>
<thead>
<tr>
<th>QUANTITY</th>
<th>DEFINITION</th>
<th>UNIT</th>
<th>NEW</th>
<th>OLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbed dose</td>
<td>Energy per unit mass</td>
<td>Gray</td>
<td>Sv</td>
<td>Rad</td>
</tr>
</tbody>
</table>

### TABLE 2. Quantities and Units Used in Radiation Protection

<table>
<thead>
<tr>
<th>QUANTITY</th>
<th>DEFINITION</th>
<th>UNIT</th>
<th>NEW</th>
<th>OLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equivalent dose (radiation weighted dose)</td>
<td>Average absorbed dose multiplied by the radiation weighting factor.</td>
<td>Sv</td>
<td>Rem</td>
<td></td>
</tr>
<tr>
<td>Effective dose</td>
<td>Sum of equivalent doses to organs and tissues exposed, each multiplied by the appropriate tissue weighting factor.</td>
<td>Sv</td>
<td>Rem</td>
<td></td>
</tr>
<tr>
<td>Committed equivalent dose</td>
<td>Equivalent dose integrated over 50 y; takes into account absorbed dose from irradiation from internally deposited radionuclides.</td>
<td>Sv</td>
<td>Rem</td>
<td></td>
</tr>
<tr>
<td>Committed effective dose</td>
<td>Effective dose integrated over 50 y; takes into account committed equivalent doses to individual organs or tissues from irradiation from internally deposited radionuclides multiplied by appropriate tissue weighting factors and then summed.</td>
<td>Sv</td>
<td>Rem</td>
<td></td>
</tr>
</tbody>
</table>

Rad indicates radiation absorbed dose; Sv, sievert; Rem, roentgen equivalent man; Person-Sv, previously designated as Man-rem, is the sum of all individual exposures or collective dose in a population (collective dose is the product of the average dose to a population and the number of persons exposed (if 100 persons receive an average equivalent dose of 0.1 Sv [10 Rem], the collective effective dose is 10 Person-Sv [1000 Man-rem]).

Caveat: effective doses allow for the comparison of doses from partial body exposures (eg, different anatomic sites), but are not appropriate estimates of absorbed radiation doses to organs or tissues. Collective doses are useful for estimating average annual population doses, but caution must be exercised when using collective dose estimates for calculating the probability of cancer in a population.

One gray (Gy) = 100 rad; 1 rad = 10 milligray or 0.01 Gy.

Sv is a metric for biological equivalent dose and mixed types of radiation exposures.

reports, based mostly on findings from radiobiology, suggest that there is substantially greater complexity regarding low dose and low-dose rate effects from nontargeted effects of low-dose radiation (eg, effects in nonirradiated cells near and at distant sites from irradiated cells).

Epidemiologic literature on low-dose and low-dose rate effects is hampered by limited statistical power at cumulative lifetime radiation levels of less than 100 millisieverts (mSv), even for very large studies. Nevertheless, despite wide confidence limits, the results of individual large and pooled studies of radiation workers reveal modest exposure-related increases in the risk of solid tumors at low-dose levels. More research is needed on radiobiologic effects along with continuing follow-up of existing and newer studies of radiation workers to clarify the shape of the dose-response relationship at low dose and low-dose rate radiation levels.

Epidemiologic studies have shown minimum latency periods of 2 to 5 years between radiation exposure and the onset of leukemias, with many of the excess leukemias occurring within the first 2 decades of exposure. There is variation in the temporal pattern of radiation-related leukemia risks between exposures in childhood and adulthood (with the decline in risk occurring sooner and in more pronounced manner for the former than the latter) and for different major subtypes of leukemia (with the excess risk of chronic myeloid leukemia decreasing substantially about 10 years after exposure, the excess risk declining much more slowly for acute myeloid leukemia, and the excess risk of acute lymphocytic leukemia decreasing with attained age based on data from follow-up of the atomic bomb survivors). Minimum latency periods are longer for solid tumors, ranging from 10 years to many years after the initial radiation exposure. Risks of most solid tumors continue to increase throughout the radiation-exposed person’s lifetime. Radiation-related cancers generally occur at the same ages as non-radiation-related cancers.

Cancer Risks Associated With External Radiation From Sources Other Than Diagnostic Radiologic Procedures: Highlights From Key Epidemiologic Studies

Much is known about cancer risks associated with a single high-dose rate external radiation exposure from studies of the Japanese atomic bomb survivors, fractionated high-dose external radiation exposures in patients treated with radiotherapy for benign or malignant disorders, and, to a lesser extent, chronic low-dose low dose rate exposures. The Life Span Study of more than 105,000 atomic bomb survivors (including 30,000 children), remains one of the richest sources of information because of the wide dose range (less than 0.005 Gy to 2-4 Gy [mean, 0.2 Gy]), wide range in age at exposure, and long-term follow-up. This study has demonstrated evidence of a linear dose response for all solid tumors combined, including a statistically significant dose response for survivors with estimated doses under 0.15 Gy (Table 3). For the 17,448 incident first primary cancers diagnosed between 1958 and 1998 (including 850 cancers or 11% diagnosed in individuals with estimated doses greater than 0.005 Gy attributable to the atomic bomb radiation exposure), significant radiation-associated excess risks were observed for most, but not all, specific types of solid tumors. Excess relative risks (ERRs) per Gy (excess compared with baseline population risks) and excess absolute rates (EARs) varied according to organ or tissue and by age at exposure. ERRs per Sv for acute lymphoid, acute myeloid, and chronic myeloid leukemias were 9.1, 3.3, and 6.2, respectively, while excess absolute rates per 10,000 person-year Sv were 0.6, 1.1, and 0.9, respectively. Minimum latency periods of 2 to 5 years were apparent for the leukemias (excluding chronic lymphocytic leukemia), but were longer for solid tumors. Excess risk persisted throughout life for most malignancies.

Among approximately 2500 atomic bomb survivors who were in utero at the time of the bombings, there was no evidence of a radiation dose-related increase in cancer mortality among persons aged younger than 15 years at the time of follow-up. In a follow-up of cancer incidence in this population during 1958 through 1997 that compared solid cancer incidence risks among in utero cohort members (based on 94 incident cancers) with risks following postnatal exposures among survivors aged younger than 6 years at the time of the bombings (based on 649 incident cancers), the investigators found that the ERRs per Sv at the same attained age of 50 years were higher for the children exposed postnatally (1.7 per Sv; 95% confidence interval [95% CI], 1.1 Sv-2.5 Sv) than for those exposed in utero (0.42 per Sv; 95% CI, 0.0 Sv to 2.0 Sv). The EARs per 10,000 person-years per Sv increased markedly with attained age among those exposed in early childhood (EAR, 6.8; 95% CI, 36-79), but showed a substantially lower increase with attained age among those exposed in utero (EAR, 6.8; 95% CI, 0.002-48). This landmark study demonstrated that in utero radiation exposure from the bombings was associated with an increased adult-onset solid tumor risk, but could not provide detailed radiation-related childhood cancer incidence risk estimates in the absence of complete incidence between 1945 and 1957 (the period after the bombings but before the establishment of population-based cancer registries in Hiroshima and Nagasaki).

The dose response patterns for cancer risks associated with high-dose fractionated radiotherapy are generally similar to those of the atomic bomb survivors, but the ERRs per Gy are lower for patients treated with high-dose fractionated radiotherapy compared with those for atomic bomb survivors, likely due to cell killing (Table 3). At high
doses, radiation kills cancer cells by irrevocably damaging DNA so the cells are nonviable, whereas at lower doses cells may undergo DNA damage, but a large proportion of irradiated cells remain viable. In radiotherapy, extensive efforts are usually made to limit lower dose “radiation scatter” to surrounding tissue, so that only a small proportion of cells irradiated receive low doses.

Nuclear workers have experienced radiation dose-related incidence and mortality risk increases for leukemias (excluding chronic lymphocytic leukemia). In the United Kingdom, incidence was slightly more elevated (ERR per Gy, 1.712; 90% CI, 0.06–4.29) than the dose-associated risks of the atomic bomb survivors (ERR per Gy, 1.4; 90% CI, 0.1–3.4). These workers also had statistically significant increases for all cancers combined other than leukemia.42,43

Dose-associated increases were also apparent for lung cancer in the 15-country study,42,43 although the associations with lung cancer may have been confounded by smoking (Table 3).

**Patterns and Trends in Diagnostic Radiologic Procedures**

Prior to 1980, exposures to the US general population from environmental sources of ionizing radiation (eg, radon, natural background gamma radiation, and cosmic rays) were estimated at about 2.8 mSv per capita versus 0.53 mSv from medical sources (the latter comprising about 15% of the estimated 3.6 mSv total).25 The estimated per capita dose from medical radiation in the United States increased approximately 600% from about 0.53 mSv in the early

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**TABLE 3. Summary of Findings From Key Epidemiological Studies Assessing Cancer Risks From Sources of External Radiation (X-Rays or Gamma Rays) Other Than Studies of Diagnostic Radiologic Procedures**

<table>
<thead>
<tr>
<th>KEY STUDIES</th>
<th>WEIGHTED ORGAN DOSES</th>
<th>HIGHLIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Japanese atomic bomb survivors</strong> Preston 200746 Preston 199444</td>
<td>40% of population &lt; 5 mGy; 3% of population &gt; 1 Gy</td>
<td>–Total solid cancer risk shows linear dose response. –Dose-response for solid cancers is significantly increased at low doses (eg, &lt; 0.15 Gy, similar doses to multiple CT scans). –Significant radiation–associated excesses seen for most solid tumors. –Risks higher for exposure at early ages (except lung, which rose with age). –Data support a radiation–associated solid tumor increase throughout life. –Approximately 11% of solid tumors due to the atomic radiation. –Significantly elevated and high ERRs per Gy for AML, ALL, and CML. –Dose-response excess persisted for several decades for ALL and CML, but peaked at 10 y after the bombings for AML. –High proportion of leukemia attributable to the atomic bomb–related radiation.</td>
</tr>
<tr>
<td><strong>Radiotherapy for benign conditions</strong> Ron 200322</td>
<td>Organ doses to cancer sites ranged from 1–15 Gy</td>
<td>–Benign conditions treated include ankylosing spondylitis, benign gynecologic disorders, and peptic ulcer and, in children and adolescents, skin hemangiomas, tinea capitis, tonsils, acne, and enlarged thymus. –Partial body irradiation, fractionated doses. –ERRs per Gy generally consistent with findings from atomic bomb survivors; significant variation in risks for specific anatomic sites, gender, age at exposure, and attained age. –Some evidence, although not consistent, that fractionation reduced risk.</td>
</tr>
<tr>
<td><strong>Radiotherapy for cancer</strong> Boice 200623</td>
<td>Organ doses to second cancer sites ranged from 2 to &gt; 200 Gy</td>
<td>–First cancers treated include uterine cervix and endometrial; Hodgkin lymphoma; non–Hodgkin lymphoma; and breast, testicular, and pediatric cancers. –Partial body irradiation, fractionated doses. –Small absolute no. of second cancers. –ERRs per Gy notably less than risks for atomic bomb survivors of similar age at exposure, likely due to cell killing; risks by anatomic site and age at exposure similar to atomic bomb survivors.</td>
</tr>
<tr>
<td><strong>Nuclear workers</strong> Cardis 200548 Cardis 200743 Muirhead 200942</td>
<td>Weighted organ doses ranged from 0 to &gt; 500 mSv; mean lifetime dose ranged from 15–25 mSv</td>
<td>–Significantly increased ERR per Sv for all cancers combined other than leukemias.42,43 –Significantly increased ERR per Sv for leukemias excluding chronic lymphocytic leukemia.42 –Significantly increased ERR per Sv for lung cancer mortality.43</td>
</tr>
</tbody>
</table>

mGy indicates milligray; Gy, gray; CT, computed tomography; RR, relative risk; ERR, excess relative risk; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; CML, chronic myeloid leukemia; mSv, millisieverts; Sv, sievert.
1980s to about 3.0 mSv in 2006 (the latter including about 1.5 mSv per capita from CT scans, 0.8 mSv from nuclear medicine procedures, 0.4 mSv from interventional procedures, and 0.3 mSv from standard radiographic procedures) (Fig. 1). Within the 25-year period, the proportion of per capita individual radiation exposure from medical sources increased from 15% to close to 50% (Fig. 1).25

Although US surveys for specific categories of radiologic procedures have been conducted periodically since the early 1950s, comprehensive assessment across different radiologic procedures has been relatively infrequent. Comparison of the estimated annual numbers and per capita doses for categories of procedures performed during 1980 to 1982 with the annual numbers performed in 2006 showed more than 2-fold increases in the total numbers of all radiographic examinations excluding dental procedures, a 20-fold increase in CT scans, a 5-fold increase in dental radiographic examinations, and a 1.5-fold increase in nuclear medicine procedures, accompanied by a notable change in the specific types of nuclear medicine procedures.25,29

Compared with an estimated 3.3 million CT scans performed between 1980 and 1982, there were an estimated 80 million CT scans performed in 2010.50 The nearly 6-fold increase in the annual estimated per capita effective dose from all sources of medical radiation between 1980 through 1982 and 2006 was due mostly to the nearly 100-fold increase in per capita dose from CT scans and the 5-fold and 2.5-fold increases from nuclear medicine and interventional procedures, respectively.25,29 Although usage has also increased in other countries, average annual per capita exposure in the United States is 50% higher than in other high-income countries (3 mSv vs 2 mSv per year, respectively).29 Recently, however, there has been evidence of a decline in the percentage of annual increase in CT imaging among Medicare fee-for-service beneficiaries from a compound annual growth rate of 9.5% during 1998 to 2005 to 4.3% during 2005 to 2008.51 Among the Medicare beneficiaries, the decline in the compound annual growth rate for all noninvasive procedures was greater for tests ordered by radiologists (from a 3.4% annual growth rate during 1998-2005 to 0.8% annually during 2005-2008) than for tests ordered by all other physicians (from a 6.6% annual growth rate during 1998-2005 to 1.8% annually during 2005-2008).

Survey data from the United Kingdom and the United States demonstrate substantial variation in estimated effective doses for different radiologic procedures (Table 4).13,52-55 For a given type of radiologic procedure, estimated effective doses differ by the anatomic site examined (Table 4), by age at examination (particularly for children and adolescents) (Table 5), and by the facility where the examination was performed (Fig. 2). Variation among hospitals in estimated effective doses associated with a specific radiologic procedure has been recognized for decades,60,61 despite early recommendations to restrict the x-ray beam to anatomic sites under study, reduce the numbers of x-ray projections, incorporate standardized protocols, and improve physician training.61 Notable variation in estimated effective doses persists as was reported in 1999 for fetal doses from radiologic examinations62 and more recently for CT scans in adults (Fig. 2).63

<table>
<thead>
<tr>
<th>TABLE 4. Typical Effective Doses From Some Medical Imaging Examinations</th>
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<tbody>
<tr>
<td><strong>TYPE OF EXAMINATION</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Radiography</td>
</tr>
<tr>
<td>Skull AP or PA</td>
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<tr>
<td>Chest PA</td>
</tr>
<tr>
<td>L-spine AP</td>
</tr>
<tr>
<td>Abdomen AP</td>
</tr>
<tr>
<td>Pelvis AP</td>
</tr>
<tr>
<td>Mammography (4 views)b</td>
</tr>
<tr>
<td>Dental radiographyc</td>
</tr>
<tr>
<td>Introral</td>
</tr>
<tr>
<td>Panoramic</td>
</tr>
<tr>
<td>Diagnostic fluoroscopy procedures</td>
</tr>
<tr>
<td>Barium swallowd</td>
</tr>
<tr>
<td>Barium enemae</td>
</tr>
<tr>
<td>Angiography: cardiacc</td>
</tr>
<tr>
<td>CTe</td>
</tr>
<tr>
<td>Head</td>
</tr>
<tr>
<td>Chest</td>
</tr>
<tr>
<td>Abdomen</td>
</tr>
<tr>
<td>Pelvis</td>
</tr>
<tr>
<td>Abdomen/pelvis</td>
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<tr>
<td>C-spine</td>
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<tr>
<td>T-spine</td>
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<tr>
<td>L-spine</td>
</tr>
</tbody>
</table>

mSv indicates millisieverts; AP, anteroposterior; PA, posteroanterior; CT, computed tomography.

*bNumber in the third column indicates the equivalent number of chest x-rays for that procedure.

cEffective dose was calculated using the mean glandular dose found in the Mammography Quality Standards Act (MQSA) inspection in 2006 in the United States.34

dAverage effective dose, health care level I countries, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) report 2000.13

eEffective dose was calculated using entrance surface dose, nationwide survey (2001-2006, United Kingdom), and effective dose conversion factor.52,53

fAverage effective doses for axial and helical scans from a nationwide survey between 2000 and 2001 in the United States.55
Epidemiologic Studies of Cancer Risks Associated With Diagnostic Radiologic Procedures

The key studies examining the association between various diagnostic radiological procedures and subsequent cancer risk are reviewed below according to age at radiation exposure. Methodologic issues related to the quality and importance of the studies include the source of information about the radiologic procedures (self-reported vs those collected from medical records), the study design (case-control vs cohort studies), the method for estimating doses (dose reconstruction for individual patients vs other approach), the timing of exposure in relation to the cancer, and adequacy of the sample size.

In Utero X-Rays and Pediatric Cancer Risks

Case-Control Studies

During the late 1940s through the 1960s, obstetricians frequently evaluated pregnancy-related medical problems with whole-fetal imaging using abdominal radiographs and gauged the likelihood of successful vaginal delivery with

### TABLE 5. Radiation Dose to Children by Age at Diagnostic Examination

<table>
<thead>
<tr>
<th>TYPE OF EXAMINATION</th>
<th>DOSE QUANTITY(^a)</th>
<th>RADIATION DOSE TO CHILDREN (BY AGE AT EXPOSURE)</th>
<th>0 YEARS</th>
<th>1 YEAR</th>
<th>5 YEARS</th>
<th>10 YEARS</th>
<th>15 YEARS</th>
<th>ADULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiography(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull AP</td>
<td>ED (mSv)</td>
<td></td>
<td>-</td>
<td>0.037</td>
<td>0.058</td>
<td>-</td>
<td>-</td>
<td>0.084</td>
</tr>
<tr>
<td>Skull LAT</td>
<td>ED (mSv)</td>
<td></td>
<td>-</td>
<td>0.025</td>
<td>0.031</td>
<td>-</td>
<td>-</td>
<td>0.041</td>
</tr>
<tr>
<td>Chest PA</td>
<td>ED (mSv)</td>
<td></td>
<td>0.023</td>
<td>0.024</td>
<td>0.037</td>
<td>0.025</td>
<td>0.026</td>
<td>0.051</td>
</tr>
<tr>
<td>Abdomen AP</td>
<td>ED (mSv)</td>
<td></td>
<td>0.077</td>
<td>0.197</td>
<td>0.355</td>
<td>0.509</td>
<td>0.897</td>
<td>2.295</td>
</tr>
<tr>
<td>Pelvis AP</td>
<td>ED (mSv)</td>
<td></td>
<td>0.085</td>
<td>0.121</td>
<td>0.230</td>
<td>0.309</td>
<td>0.556</td>
<td>1.783</td>
</tr>
<tr>
<td>Dental radiography(^c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoral</td>
<td>ED (mSv)</td>
<td></td>
<td></td>
<td>0.008(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panoramic</td>
<td>ED (mSv)</td>
<td></td>
<td></td>
<td>0.015(^d)</td>
<td></td>
<td></td>
<td></td>
<td>0.015</td>
</tr>
<tr>
<td>Diagnostic fluoroscopy procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCU(^f)</td>
<td>ED (mSv)</td>
<td>0.807</td>
<td>0.763</td>
<td>0.688</td>
<td>0.640</td>
<td>0.677</td>
<td>2.789</td>
<td></td>
</tr>
<tr>
<td>Barium swallow(^g)</td>
<td>ED (mSv)</td>
<td>0.645</td>
<td>0.589</td>
<td>0.303</td>
<td>0.760</td>
<td>0.581</td>
<td>1.632</td>
<td></td>
</tr>
<tr>
<td>Barium meal(^h)</td>
<td>ED (mSv)</td>
<td>2.209</td>
<td>2.226</td>
<td>1.427</td>
<td>2.137</td>
<td>2.386</td>
<td>5.158</td>
<td></td>
</tr>
<tr>
<td>Cardiac-ASD occlusion(^e)</td>
<td>ED (mSv)</td>
<td></td>
<td></td>
<td>3.88(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac-PDA occlusion(^e)</td>
<td>ED (mSv)</td>
<td></td>
<td></td>
<td>3.21(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac-VSD occlusion(^e)</td>
<td>ED (mSv)</td>
<td></td>
<td></td>
<td>12.1(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT(^f)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>ED (mSv)</td>
<td>2.3</td>
<td>2.2</td>
<td>1.9</td>
<td>2.0</td>
<td>2.2</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Facial bone/sinuses</td>
<td>ED (mSv)</td>
<td>1.4</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>ED (mSv)</td>
<td>1.9</td>
<td>2.2</td>
<td>2.5</td>
<td>3.0</td>
<td>3.3</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Entire abdomen</td>
<td>ED (mSv)</td>
<td>3.6</td>
<td>4.8</td>
<td>5.4</td>
<td>5.8</td>
<td>6.7</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>ED (mSv)</td>
<td>4.4</td>
<td>11.4</td>
<td>8</td>
<td>7.6</td>
<td>6.9</td>
<td>10.1</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Dosimetric quantities are all shown as the ED.


\(^c\)Source: Hart D, Hillier MC. Dose to Patients From Medical X-Ray Examinations in the UK-2000 Review. Chilton, UK: National Radiological Protection Board; 2007.\(^52\)

\(^d\)Age is not specified.

\(^e\)Source: Onnasch DG, Schroder FK, Fischer G, Kramer HH. Diagnostic reference levels and effective dose in paediatric cardiac catheterization. *Br J Radiol*. 2007;80:177-185. The mean age of patients is 2.5 years.

\(^f\)Source: Galanski M, Nagel HD, Stamm G. Paediatric CT Exposure Practice in the Federal Republic of Germany–Results of a Nation-Wide Survey in 2005/2006. Hannover, Germany: Hannover Medical School; 2006.\(^59\) Radiation doses to adults are based on a German nationwide survey on multislice CT.\(^59\) The radiation dose in each age group category is the dose administered to pediatric patients who are newborn (the 0-y category), those ages >0-1 (the 1-y category), those ages 2 to 5 y (the 5-y category), those ages 6 to 10 y (the 10-y category), and those ages 11 to 15 y (the 15-y category).
radiographic imaging of the maternal pelvis and fetal structures within the pelvis (pelvimetry). More than 50 years ago, Stewart et al, in the large Oxford Survey of Childhood Cancers (OSCC) case-control study, described a 2-fold statistically significantly higher risk of total pediatric cancer mortality in the offspring of women who underwent diagnostic x-ray procedures compared with risk in the offspring of women who did not undergo radiographic procedures during pregnancy. Radiation doses to maternal and fetal gonads from pelvimetry based on nationwide UK surveys in the 1950s ranged from 1.4 mGy to 22 mGy per exposure, depending upon the projection and number of exposures. There was also notable variation within and among countries and over time in the proportion of pregnant women undergoing pelvimetry or abdominal x-rays. Although the interview-based 2-fold increase in risk reported by Stewart et al was initially received with skepticism, more notice was taken when the significant risk excess (RR, 1.5; 95% CI, 1.19-1.96), albeit slightly lower, risk based on the 4052 pediatric leukemia cases in the OSCC (RR, 1.39; 95% CI, 1.31-1.47) persisted after the accrual of more than 15,000 pediatric cancer cases in the OSCC between 1953 and 1981, maternal self-reports correlated well with radiologic reports, and a similar 1.4-fold significantly increased risk of total pediatric cancer based on medical records was reported in the offspring of mothers undergoing prenatal radiographic examinations in the northeast United States. Subsequently, other studies from the United Kingdom, the United States, Finland, and Sweden replicated the findings.

A 2008 meta-analysis of 32 case-control studies of pediatric leukemia (excluding the hypothesis-generating OSCC study) revealed a similar (RR, 1.32; 95% CI, 1.19-1.46), albeit slightly lower, risk based on the 4052 pediatric leukemia cases in the OSCC (RR, 1.49; 95% CI, 1.33-1.67). The risk of pediatric leukemia from fetal diagnostic x-ray exposure in case-control studies of twins was comparable to the risks observed in singletons. In the OSCC, the estimated RR for all solid tumors (1.47; 95% CI, 1.34-1.62) was similar to the risk of leukemia (RR, 1.49; 95% CI, 1.33-1.67). A few early studies reported modest 20% to 30% increased risks of pediatric central nervous system tumors in the offspring of mothers undergoing diagnostic radiologic procedures with abdominal radiation, but more recent studies generally found no increase in risk. A limited number of case-control studies with small numbers of cases have assessed the risks of other pediatric tumors associated with in utero diagnostic x-rays.

OSCC data showed a dramatically declining risk of total pediatric cancer associated with fetal radiation exposure over time, from a 5.4-fold excess among offspring born between 1946 and 1947 to a 1.3-fold increase among children born between 1962 and 1963. Compared with the 1.5-fold to 2.2-fold increased risk of pediatric acute lymphoblastic leukemia in the offspring of mothers undergoing abdominal or pelvic diagnostic x-ray procedures reported in earlier studies, risks were substantially lower or not increased in more recent studies, possibly due to decreases in estimated radiation dose levels.
Cohort Studies

Cohort studies of pediatric cancer risks associated with in utero diagnostic x-rays have included a few hundred to 39,166 exposed children, but the findings were based on 13 or fewer total pediatric cancer cases and 9 or fewer pediatric leukemia cases in each cohort. Summary RR were initially reported by Doll and Wakeford\(^68\) (RR, 1.2; 95% CI, 0.7-2.0) and subsequently by the International Commission on Radiological Protection (ICRP) 2003 report\(^80\) for a larger number of studies (RR, 1.08; 95% CI, 0.78-1.50). The estimated RRs for the combined cohort studies were not significantly increased, although the confidence intervals were compatible with both the 40% increase from the case-control studies and with a decreased risk due to limited power and substantial uncertainty.\(^68,80\) A recent record linkage study from Ontario that reported a nonsignificantly reduced risk of total pediatric cancer (based on 4 childhood cancer cases) in the offspring of 5590 mothers exposed to major radiologic procedures in pregnancy compared with cancer occurrence in the offspring of 1.83 million non-exposed mothers also had wide 95% CIs.\(^81\)

Because the association between in utero diagnostic x-ray exposure and pediatric cancer risk could be confounded by maternal or fetal medical conditions prompting diagnostic x-ray examinations, epidemiologic studies of twins were recommended to clarify whether confounding could explain the association since a high proportion of twins underwent pelvimetry in early years to determine fetal positioning rather than for medical conditions.\(^82\) Cancer risks have been investigated in twin cohorts ranging in size from 13,000 to more than 125,000, with total pediatric cancer cases ranging from 14 to 166 and pediatric leukemia cases ranging from 3 to 55.\(^33-39\) RRs ranged from 0.70 to 0.96 for total cancer and from 0.7 to 1.14 for leukemia. Cancer risks in twins have not changed over time as pelvimetry has been replaced with ultrasonography,\(^85\) but lower pediatric leukemia risks in twins compared with singletons may reflect biologic or clinical characteristics of twins such as low birth weight, intrauterine growth restriction, 5-fold higher mortality in the first year of life, or genetic factors, which may outweigh potentially carcinogenic risks associated with in utero radiation exposure.\(^87,90\)

Confounding and Uncertainties

To address concerns that the observed associations between fetal diagnostic x-ray exposure and elevated pediatric cancer risk in offspring might be confounded by medical indications for the x-rays, additional analyses were undertaken that demonstrated that the associations were still apparent when the reasons for the diagnostic radiologic examinations were considered.\(^67\) In the medical record-based northeast US study, the associations were specific for childhood cancer and not other causes of death in children, and there was no evidence of confounding by many other factors.\(^17\) The studies of diagnostic x-rays in utero and the risk of pediatric leukemia and other cancers are characterized by several uncertainties, the most important being a lack of dose measurement data.\(^18,68\)

Summary of Findings From Studies of In Utero X-Rays and Cancer Risks in Offspring

In utero diagnostic x-rays in earlier decades have been consistently linked with a small excess of pediatric leukemia in offspring. There continues to be debate about whether a radiation dose estimated to be approximately 10 mGy could give rise to cancer.\(^91\) Doll and Wakeford had previously estimated that the lifetime excess risk of cancer for those exposed in utero was 6%,\(^68\) which is 2-fold to 3-fold higher than the ICRP lifetime excess risk estimate for exposure in childhood.\(^80\) but data from the recent follow-up of the atomic bomb survivors comparing ERRs and EARs of those children exposed in utero and those exposed in early childhood do not support a projection of a higher lifetime risk for the former compared with the latter.\(^47\) Additional follow-up is needed to quantify lifetime risks in the atomic bomb survivors exposed early in life. Although ultrasound replaced abdominal x-rays and pelvimetry several decades ago, there recently have been reports of increasing levels of radiologic imaging in pregnant women in the United States. Investigators leading a large survey at one institution reported that CT increased by 25% per year and nuclear medicine by 12% per year during 1997 through 2006.\(^92\)

Understanding the cancer risks from in utero exposures, therefore, remains important.

Childhood and Adolescent X-Rays and Pediatric and Lifetime Cancer Risks

Early Postnatal X-Rays and Pediatric Cancer Risks

The OSCC found no association between early life diagnostic exposure and risks of total pediatric cancer as reported in interviews of mothers.\(^16\) Postnatal diagnostic x-rays of children born between 1980 and 1983 in the United Kingdom were associated with a nonsignificant 2-fold increase (95% CI, 0.32-12.51) of childhood cancer risk based on interview data, but this association was largely attenuated (RR, 1.11; 95% CI, 0.32-3.63) when risks were recalculated for maternal reports of radiologic examinations that were confirmed in medical records.\(^93\) More recently, a nonsignificant modest increase in the risk of all pediatric cancer (RR, 1.19; 95% CI, 0.82-1.74) was found in 2690 UK childhood cancer patients born between 1976 and 1996 based on evaluation of medical records.\(^79\) There was a slight excess of cancer in 4891 Canadian children with congenital heart disease who underwent cardiac catheterization during 1946 through 1968, and additional follow-up of a subset revealed a nonsignificant 60% excess of leukemia (90% CI, 0.43-4.14 based on 3 cases among 5 total pediatric
cancer cases). Among 675 Israeli children who underwent cardiac catheterization for congenital anomalies during 1950 through 1970, there was a significant cancer excess (observed vs expected, 2.3; 95% CI, 1.2–4.1) due to increased risks of lymphomas and melanomas, based on very small numbers of these malignancies.

While 2 interview-based studies of early postnatal diagnostic x-rays found a significantly elevated risk of leukemia, and a third observed a significant excess of acute lymphoblastic leukemia (but not acute myeloid leukemia) with exposure to diagnostic radiation, other investigations, including studies based on medical record assessment, have not found significant increases. Few studies have investigated whether early postnatal exposure to diagnostic x-rays was linked with an increased risk of specific subtypes of pediatric acute lymphocytic leukemia, but Shu et al found that the risk was significantly elevated for pre-B-cell acute lymphoblastic leukemia, and Bartley et al reported that the risk was significantly increased for B-cell acute lymphocytic leukemia. Postnatal radiation exposure from diagnostic radiographs has generally not been linked to an increased risk of childhood brain tumors. There have been relatively few studies of pediatric cancers following postnatal radiation other than leukemia and brain tumors and most have had small numbers of exposed cases, including 2 studies that found an increased risk of lymphoma.

**Childhood or Adolescent Diagnostic Radiologic and Other Radiation Exposures and Lifetime Cancer Risks**

Epidemiologic studies of atomic bomb survivors exposed as young children and children treated with radiotherapy for benign conditions or cancer found that children exposed at young ages to ionizing radiation were at an increased risk of developing radiation-related cancer later in life. Other evidence also indicates that exposure to diagnostic radiation in childhood or adolescence may have implications for lifetime cancer risk. Repeated diagnostic radiology examinations in adolescents and young women monitored for scoliosis have been associated with increased breast cancer risks later in life. The ERR per Gy for breast cancer incidence was 2.86 ($P = .058$) in those monitored for scoliosis (mean dose to the breast was 120 mGy), and risks remained elevated for at least 5 decades following exposure. Risks of lung cancer and leukemia, however, were not elevated in either of these 2 groups of patients.

**Summary of Findings From Studies of Postnatal X-Rays and Cancer Risks**

Overall, studies of pediatric cancer risks in children undergoing radiographic examinations have produced ambivalent results, perhaps due in part to methodologic limitations or differences (eg, insufficient age matching, recall bias, incorporation of varying latency periods, differing types of radiologic examinations evaluated, and reductions in radiation doses over time for standard radiologic procedures). In addition, if diagnostic radiation exposures are truly associated with very small risk increases, many epidemiologic studies may be too small to detect these increases. Few epidemiologic studies of diagnostic radiation exposures in young children have followed the population for sufficiently long periods to assess risks in adulthood. There are major initiatives currently underway around the world, however, to assess the cancer risks from CT scans received in childhood. These studies address many of the limitations described above.

**Adult X-Rays and Cancer Risks**

**Repeated Fluoroscopic Imaging Procedures and Cancer Risks**

There have been several large retrospective cohort studies of patients with tuberculosis who were monitored frequently using fluoroscopy. There was a wide range in the number of examinations. The mean dose to the most highly exposed organs (the breast and the lung) was close to 1 Gy. Significant dose–response relationships were found for breast cancer (RR, 1.29; 95% CI, 1.1–1.5), but there was no evidence of an increased risk of lung cancer. There have been no other epidemiologic studies assessing cancer risks in patients undergoing repeated fluoroscopic imaging procedures. Epidemiologic studies of adults undergoing non-fluoroscopic imaging procedures have provided more limited information due to the limited size of such studies, the lower sensitivity of adults to the carcinogenic effects of ionizing radiation compared with children, the lack of individual patient dosimetry, and the potential for recall bias. Findings from larger studies characterized by stronger methodology and efforts to minimize biases are summarized below.

**Adult Diagnostic X-Rays and Leukemia Risks**

In a large case-control study conducted in a health maintenance organization in which over 25,000 x-ray procedures were abstracted from medical records and each x-ray procedure was assigned a score based on estimated bone marrow dose, there were small, nonsignificant elevations in risk of leukemias other than chronic lymphocytic leukemia using different lag periods (3-month lag: RR, 1.17 [95% CI, 0.8–1.8]; 2-year lag: RR, 1.42 [95% CI, 0.9–2.2]; and 5-year lag: RR, 1.04 [95% CI, 0.6–1.8]), but no evidence of dose–response relationships. Preston-Martin and Pogoda found that risks rose with increasing estimated doses to bone marrow to a 2.4-fold excess risk associated with an estimated dose of 20 mGy in the 3 to 20 years prior to diagnosis in a medical record–based case-control study of adult-onset acute myeloid leukemia in Los Angeles that utilized a unique database of estimated doses and dose ranges based on review of the dosimetry literature and consultation with radiology experts. Radiographic procedures of the gastrointestinal tract and multiple spinal x-rays were linked with an increased risk of chronic myeloid leukemia in a case-control study in
Los Angeles.\textsuperscript{108} Three of 4 earlier studies of chronic myeloid leukemia and diagnostic radiographic procedures (2 of which examined medical records) found evidence of small risks and one found a dose-response relationship with an increasing number of x-ray films in the 20 years prior to diagnosis.\textsuperscript{108}

**Adult Diagnostic X-Rays and Cancers Other Than Leukemia**

From the large case-control study by Boice et al, small, non-significant increases were apparent for multiple myeloma for all lag periods, and dose-response trends approached statistical significance due to high RRs of patients in the highest exposure score category. There was no significant dose-response relationship for non-Hodgkin lymphoma.\textsuperscript{109} In Sweden, the cumulative number of x-ray examinations (derived from medical record review) was not linked with thyroid cancer risk.\textsuperscript{110} Meningiomas\textsuperscript{111,112} and parotid tumors in adults in Los Angeles\textsuperscript{113} were associated with full-mouth and substantial numbers of dental x-rays prior to age 20 years or before 1945. Comparison of interview data with dental records showed similar levels of agreement for cases and controls, suggesting that the findings were not due to recall bias.\textsuperscript{114}

**Summary of Findings From Studies of Adult X-Rays and Cancer Risks**

Overall, the most compelling results are the significant dose response associations with breast cancer, but not lung cancer, in the cohort studies of patients undergoing repeated fluoroscopic imaging examinations for tuberculosis. Inconsistent findings, limited numbers of epidemiologic studies, and relatively small numbers of substantially exposed leukemia cases other than chronic lymphocytic leukemia make it difficult to draw clear conclusions about diagnostic radiography and the risk of leukemia other than chronic lymphocytic leukemia. Limited data suggest a possible risk of chronic myeloid leukemia. There are too few studies examining risks of non-Hodgkin lymphoma, multiple myeloma, thyroid cancer, parotid tumors, or meningiomas to draw conclusions. Recently, a statistical association was reported between chromosome translocation frequencies in cultures of peripheral blood lymphocytes and increasing radiation dose score based on numbers and types of diagnostic x-ray examinations in a cohort of US radiologic technologists.\textsuperscript{115,116} Mechanistic approaches in conjunction with epidemiologic and genetic studies in selected populations may provide insights about the role of low-dose radiation procedures and genetic susceptibility in breast, thyroid, and other radiogenic cancer risks.

**Animal Studies**

**Results of Key Studies**

Excess risks of liver, pituitary, and ovarian cancers have been reported in the offspring of pregnant mice who were irradiated with a single whole-body dose of 0.3 to 2.7 Gy in utero on days 16 to 18 postcoitus.\textsuperscript{117-119} In contrast, the offspring of mice irradiated with 1.0 Gy on each day of gestation experienced no significant increase in their incidence of tumors as adults.\textsuperscript{120} The offspring of 1343 pregnant Beagle dogs irradiated with a single dose of 0.16 or 0.81 Gy on days 8, 28, or 55 after breeding and 2, 70, and 365 days postpartum (120 dogs in each dose and treatment day group) had a significant increase in their incidence of benign and malignant neoplasms, including fatal malignancies at young ages and during their lifetime.\textsuperscript{121} Statistically significant increases in the risk of lymphoma were seen in the beagles irradiated at 55 days postcoitus and significant increases of hemangiosarcomas occurred at 8 and 55 days postcoitus, respectively, but a significantly increasing trend with increasing dose was seen only for hemangiosarcoma among dogs irradiated on day 8 postcoitus.\textsuperscript{121}

Studies examining the effects of radiation exposure of 0.5 to 3 Gy in mice during gestation have demonstrated various effects consistent with radiation-related genomic instability in fetal murine hematopoietic cells that are transferred though cell migration to postnatal bone marrow and seen subsequently as chromosomal abnormalities in adult bone marrow, but to date studies have not shown the induction of leukemia from chromosomal abnormalities in adult revealed that cells with these aberrations are eliminated during the early postnatal stage.\textsuperscript{122} Efforts to track explicit chromosomal aberrations from fetus to adult revealed that cells with these aberrations are eliminated during the early postnatal stage.\textsuperscript{123} Nakano et al\textsuperscript{124} showed that mean translocation frequencies in peripheral blood T cells, spleen cells, and bone marrow cells evaluated in mice at 20 weeks of age were very low when the mice had been exposed to 1 or 2 Gy of x-rays during the fetal or early postnatal stages, but translocation frequencies increased with increasing age at irradiation and then plateaued for mice irradiated at 6 weeks of age or older. These findings in mice were consistent with the absence of a radiation dose-related increase in the frequency of chromosome translocations in atomic bomb survivors exposed in utero (and studied at age 40 years), although the mothers of these offspring were found to have a radiation dose-associated increase in chromosomal translocations.\textsuperscript{125}

**Summary of Animal Studies and Future Directions for Experimental Studies**

Studies of laboratory animals have demonstrated the shape of radiation-associated dose-response curves for cancer over a broad range of doses; carcinogenic effects of acute, single-dose versus fractionated or protracted doses; the radiation-related dose response for cancer according to age at exposure, sex, organ irradiated, genetic background, physiological condition, and environment of the animals; and cellular and molecular mechanisms of carcinogenesis.\textsuperscript{39} Unfortunately, few studies have exposed animals to radiation levels in the range
of diagnostic radiologic procedures (less than 0.10 Gy). In more recent years, investigators have developed experimental models to study the effects of radiation, cellular interactions, and mechanisms at the cancer progenitor cell level for studies of carcinogenic initiation. From these studies, accumulating data suggest that processes other than the induction of specific locus mutations may be important. Such processes may include increased transcription of specific genes, altered DNA methylation, delayed genomic instability (e.g., radiation-induced chromosomal alterations, changes in ploidy, or micro- and microsatellite instabilities or other changes occurring at delayed times after irradiation and manifest in the progeny of exposed cells), and bystander effects (e.g., nontargeted cellular effects usually associated with direct exposure to ionizing radiation but occurring in nonirradiated cells).39

Risk Projection Studies
Rationale and Approach to Risk Projection
As described above, because the risks to individuals from diagnostic radiation exposures are generally small, it is often difficult to study them directly. However, because of the large number of people exposed annually, even small risks could translate into a considerable number of future cancers. Risk projection models, which utilize the wealth of existing information on the long-term cancer risks after radiation exposure, can provide a more timely assessment of the magnitude of the potential risks. A number of expert committees have developed methodologies to estimate the future cancer risks from low-dose radiation exposures. The National Academy of Science BEIR VII committee was the most recent to develop models for the US population,38 and the United Nations Scientific Committee on the Effects of Atomic Radiation13 has also published models for a number of different populations. These reports were used in most of the examples described below.

Based on the frequency of x-ray use in the United States in the early 1990s, Berrington de Gonzalez and Darby126 estimated that about 1% of cancers in the United States might be related to diagnostic x-rays and CT scans. At that time, only very basic US survey data were available. Using newly available detailed estimates of the frequency of diagnostic medical radiation exposures in the United States25 and state-of-the-art risk projection models for cancer risks associated with low-dose radiation exposure to the US population,38 they recently published updated risk projections for current levels of diagnostic radiation exposures in the United States.127,128 The projected levels of risk and confidence limits assume a linear dose-response relationship for solid tumors, although there is uncertainty about the magnitude of the risk at low doses.41

Diagnostic Radiologic Procedures
These recent estimates suggest that the 70 million CT scans performed in the United States in 2007 could result in approximately 29,000 future cancers (95% uncertainty limits, 15,000–45,000).128 One-third of the projected cancers were from scans performed at ages 35 to 54 years, compared with 15% from scans performed before age 18 years; abdomen/pelvis scans in adults contributed almost one-half of the total risk. If CT scan use remains at the current level, these results suggest that eventually about 2% (95% uncertainty limits, 1%-3%) of the 1.4 million cancers diagnosed annually in the United States129 could be related to CT scans.128 The most common projected cancers in decreasing order were lung cancer, colon cancer, and leukemias.

Screening Procedures
Risk projection models have been used in a number of studies to estimate the potential radiation risks from repeated screening. The results of those studies (e.g., screening frequencies and age ranges) are shown in Table 6.130-134 The risks range from about 40 radiation-related cancers per 100,000 screened for annual coronary artery calcification from ages 45 to 70 years131 to 1900 cancers per 100,000 for annual whole-body CT screening from ages 45 to 70 years.133

The decision to expose large numbers of asymptomatic individuals to radiation from screening tests such as CT colonography needs careful assessment since most of the persons screened will not develop the disease of interest. In general, the benefits, where established, should outweigh all risks, including the radiation risks from the radiologic screening test. For example, the mortality reduction from regular mammographic screening in women aged 50 years or older is much greater than the estimated risk of radiation-related breast cancer.134 This may not be the case, however, for some screening tests or for screening at ages younger than the recommended ages because the radiation risks are higher but the absolute benefits from screening are typically lower.135 Whole-body CT screening is not currently recommended as a screening tool as no clear benefit has been established.

Genetic Susceptibility and Radiation-Related Cancer Risks
Patients With Chromosome Instability
Evidence for an association between radiation and cancer in genetically susceptible populations with radiation sensitivity comes primarily from studies of individuals with chromosome instability disorders, such as ataxia telangiectasia (AT) and Nijmegen breakage syndrome (NBS).136-138 These rare, autosomal, recessive diseases predispose to malignancies (leukemia and lymphoma for AT and B-cell lymphoma prior to age 15 years for NBS) and in vitro
studies indicate that individuals with these disorders are unusually sensitive to ionizing radiation. Clinical sensitivity to radiation has been observed following radiotherapy in these individuals, but it is not known whether they are unusually sensitive to the lower radiation doses typically received from diagnostic exposures. Defects in DNA repair genes may predispose individuals to radiogenic cancer or lower the threshold for the development of deterministic effects. Patients with serious and unanticipated radiation injuries may be among the 1% of the population that is heterozygous for the AT mutated (ATM) gene, an autosomal recessive gene responsible for AT, or may harbor some other ATM abnormality. Patients with with familial polyposis, Gardner syndrome, hereditary malignant melanoma, and dysplastic nevus syndrome may also be characterized by increased radiation sensitivity.

Patients With Hereditary Syndromes

Increased cancer risks associated with radiotherapy have been noted for individuals with hereditary cancer syndromes including retinoblastoma (Rb), neurofibromatosis type 1 (NF1), Li-Fraumeni syndrome (LFS), and nevoid basal cell carcinoma syndrome (NBCCS). Genetic predisposition has a substantial impact on cancer risk in these populations, which is further increased by radiotherapy. A study of patients with hereditary Rb found a notably and statistically significant radiation dose response for bone and soft tissue sarcomas. Patients with NF1 who were irradiated for optic pathway gliomas are at increased risks of developing other cancers including gliomas, soft tissue sarcomas, leukemia, and malignant peripheral nerve sheath tumors. Elevated risks of developing second and third cancers were observed in a cohort of 200 LFS family members, especially children, possibly related to radiotherapy. Children with NBCCS are very sensitive to radiation and develop multiple basal cell cancers in irradiated areas. Due to improved survival, patients with these syndromes are at risk of second and third cancers, and they generally undergo periodic imaging to detect new tumors. Although the association between diagnostic radiation and cancer risk has not been evaluated in these populations, magnetic resonance imaging (MRI) scans have been recommended in place of imaging studies that produce ionizing radiation exposures to follow up symptoms, evaluate abnormal physical findings, or monitor the effects of cancer treatment, particularly in Rb survivors and children with NBCCS, especially those who have been diagnosed with medulloblastoma. In contrast, [18F]-fluorodeoxyglucose (18FDG )-PET scans have been recommended for the detection of tumors in patients with LFS and NF1.

Low Penetrance Genetic Alleles, Radiation Exposure, and Cancer Risk

Despite much interest in the possibility that common genetic variants confer an increased risk of radiation-induced cancer, there has been little empirical evidence to date, particularly within the context of diagnostic radiation. One study of childhood leukemia reported a potential modification of the relationship between diagnostic x-rays and risk of leukemia by variants in the DNA mismatch repair genes human mutS homolog 3 (hMSH3) (exon23 variant) and human MutL homolog 1 (hMLH1) (exon8 variant), but results from the study were sex-specific and were not consistent between the first and second phases of the study. A population-based study of breast cancer and a series of nested case-control studies in US radiologic technologists have suggested that common variants in genes involved in DNA damage repair,

|| STUDY | SCREENING TEST | FREQUENCY | AGE, YEARS | RADIATION-RELATED CANCERS (PER 100,000 SCREENED) |
|---|---|---|---|---|
| Brenner 2004¹³⁰ | Lung CT (smokers) | Annual | 50-70 | 230 (males) 850 (females) |
| Kim 2009¹³¹ | Coronary artery calcification CT | Annual | 45-70 (males) | 40 (males) 55-70 (females) 60 (females) |
| Berrington de Gonzalez 2011¹³² | CT colonography | Every 5 y | 50-70 | 150 |
| Brenner & Eliston, 2004¹³³ | Whole-body CT | Annual | 45-70 | 900 |
| Yaffe & Mainprize, 2011¹³⁴ | Mammography | Annual at age <55 y | 45-74 | 9 (females) |
| | | Biannual at age ≥55 y |

CT indicates computed tomography.
apoptosis, and proliferation \(^{157}\) may alter the risk of radiation-related breast cancer from diagnostic radiation procedures, but these results need to be replicated. Similarly, there is some indication that single nucleotide polymorphisms in the O 6-methylguanine DNA methyltransferase (\(MGMT\)) and poly (ADP-ribose) polymerase 1 (\(PARP1\)) DNA repair genes could modify the relationship between diagnostic radiation exposure and risk of glioma, \(^{158}\) but this has not been reported in other studies.

**Summary of Findings on Genetic Susceptibility and Cancer Risk**

A few rare genetic variants associated with human cancer susceptibility syndromes appear to increase radiation susceptibility in individuals with chromosome instability disorders and certain hereditary cancer syndromes. Although these syndromes affect only a small proportion of the general population, it is important to identify such individuals and reduce their medical radiation exposure to the extent possible. Genetic pathways including DNA damage repair, radiation fibrogenesis, oxidative stress, and endothelial cell damage have been implicated in cell, tissue, and gene studies of radiosensitivity, \(^{159}\) indicating that at least some part of the genetic contribution defining radiation susceptibility is likely to be polygenic, with elevated risk resulting from the inheritance of several low-penetrance risk alleles (the “common-variant-common-disease” model). While common genetic variation underlying this susceptibility is likely, identifying this variation is not straightforward. It is essential that future studies addressing this question be large in size and have sufficient power to adequately address variation in demographic factors, and also include high-quality radiation exposure information.

**How Do Radiation Exposures From Imaging Procedures Compare With Radiation Levels Associated With Cancer Risks?**

Radiation dose levels associated with significantly increased cancer risks are shown in Table 7. \(^{18,20,42-44,46,66,102,160-162}\) These data are derived from epidemiologic studies assessing low-dose radiation and cancer risks. Based on epidemiologic data, an international, multidisciplinary group of radiation science experts concluded that the lowest dose of x- or gamma radiation for which there is good evidence of increased cancer risks in humans is approximately 10 to 50 mSv for an acute exposure and approximately 50 to 100 mSv for a protracted exposure, but they recognized the uncertainties of these estimates and the difficulties of increasing precision in estimating radiation dose response. \(^{71}\) Data from the most recent follow-up of solid cancer incidence in the atomic bomb survivors revealed a statistically significant dose response in the range of 0 to 150 mGy, and the pattern of the trend at low doses was consistent with the trend for the full dose range. \(^{46}\) Although a linear extrapolation of cancer risks from intermediate to low radiation doses appears to be the most reasonable hypothesis, it is acknowledged that there is uncertainty about the true relationship. \(^{41}\)

From Table 4, the range of estimated effective doses from a single CT scan is 2 to 15 mSv. Mettler et al have reported that 30% of patients who undergo CT scans have at least 3 scans, 7% have at least 5 scans, and 4% have at least 9 scans. \(^{26}\) Patients who undergo multiple CT scans, as described in studies assessing the use of CT among patients with a wide range of medical disorders, \(^{163-166}\) may be exposed to radiation doses associated with increased cancer risks. A single CT examination may comprise multiple CT scan sequences. Data from 2008 Medicare claims revealed that some hospitals were performing 2-scan sequences for a chest CT examination more than 80% of the time, even though the national average is 5.4%. Overall, 2009 Medicare data showed little change from the 2008 data. \(^{167}\)

**Strategies For Reducing Radiation Exposure From Diagnostic Imaging Procedures**

**Key Concepts**

**Justification**

The referring medical practitioner is responsible for ensuring that a diagnostic procedure involving ionizing radiation is necessary for a patient’s care and that the radiation dose from the procedure is expected to do more good than harm, a concept designated as *justification* by the ICRP. \(^{31}\)

**Optimization**

The radiological medical practitioner (who is not always a radiologist) is responsible for ensuring that the radiologic procedure provides images adequate for diagnosis and treatment while keeping the radiation dose as low as reasonably achievable (ALARA), a concept designated as *optimization* by the ICRP. \(^{31}\) Optimization requires identifying imaging parameters and using procedures and protocols to produce the clinically required information while keeping radiation doses as low as possible.

In addition, the imaging equipment must be properly set up and maintained. To achieve optimization, radiological medical practitioners and radiologic technologists, with substantial input from manufacturers, must work closely with medical physicists to ensure rigorous oversight of radiation-producing imaging units. This includes accuracy of settings, safeguards, calibration, and maintenance, as highlighted in reports of excess radiation during CT brain perfusion scans. \(^{168,169}\) In the United States, there are 2 more avenues for optimization of the CT unit. One is the yearly state requirements for the evaluation of dose by a physicist and by inspections. For CT, accreditation of technologists is rapidly becoming mandatory, while
accreditation of the CT unit is now voluntary but will be mandated for payment by Medicare in 2014.

Implementation of Justification and Optimization

Referring medical practitioners need guidance to determine whether an imaging study is needed and, if an imaging study is required, which type of imaging study will yield the necessary clinical information at the lowest achievable radiation dose. Unfortunately, it has been well documented that many physicians are often not conversant with the pros and cons of various imaging modalities, with the types of imaging modalities producing ionizing radiation exposure, or with the levels of radiation associated with specific imaging modalities.\textsuperscript{170-172} Therefore, one of the most important roles of the radiological medical practitioner is to provide advice to the referring medical practitioner about the appropriate test for the patient. The advice from the radiological medical practitioner can be provided in several ways. An efficient method would be for the radiological medical practitioner to screen requests for “high-dose” examinations such as CT and, if the appropriate indication is not given or if the patient has had the same or similar radiologic procedures recently, to contact the referring medical practitioner and discuss the case.

Reducing radiation exposure from diagnostic procedures is a shared responsibility of the referring medical practitioner and the radiological medical practitioner.\textsuperscript{173} To assist referring medical practitioners in decision-making about imaging in the management of patients, the American College of Radiology (ACR)\textsuperscript{174,175} and the American College of Cardiology (ACC) in collaboration with other professional societies\textsuperscript{176,177} in the United States and the Royal College of Radiologists\textsuperscript{178} in the United Kingdom have developed evidence- and/or consensus-based guidelines. These guidelines, produced by a panel of experts, generally take the form of identifying which modalities are most appropriate. Below we summarize key elements of the strategy to guide referring medical practitioners in selecting the optimal imaging tests needed for clinical diagnosis and

### TABLE 7. Radiation Dose Levels Associated With Increased Cancer Risks in Epidemiologic Studies Assessing Low-Dose Radiation and Cancer Risk

<table>
<thead>
<tr>
<th>STUDY</th>
<th>POPULATION SIZE</th>
<th>MEAN DOSE, mGy</th>
<th>CANCER OUTCOME</th>
<th>ERR/Gy (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preston 2007\textsuperscript{46}</td>
<td>Atomic bomb survivors</td>
<td>30.8 weighted colon</td>
<td>All solid cancers, adult incidence</td>
<td>0.47 (0.40-0.54) for total population</td>
</tr>
<tr>
<td></td>
<td>All = 105,427</td>
<td></td>
<td></td>
<td>Statistically significant dose response when analyses limited to cohort members with doses in range of 0-150 mGy</td>
</tr>
<tr>
<td>Cardis 2007\textsuperscript{43}</td>
<td>15-country nuclear workers = 407,391</td>
<td>20 weighted colon</td>
<td>All solid cancer, mortality</td>
<td>0.87 (0.03-1.9)</td>
</tr>
<tr>
<td>Muirhead 2009\textsuperscript{42}</td>
<td>NRRW radiation workers = 174,541</td>
<td>24.9 weighted colon</td>
<td>All solid cancers, mortality</td>
<td>0.275 (0.02-0.56)</td>
</tr>
<tr>
<td>Krestinina 2005\textsuperscript{160}</td>
<td>Population radionuclide waste = 29,873</td>
<td>30 stomach</td>
<td>All solid cancers, mortality</td>
<td>0.92 (0.2-1.7)</td>
</tr>
<tr>
<td>Krestinina 2007\textsuperscript{161}</td>
<td>Population radionuclide waste = 17,433</td>
<td>40 stomach</td>
<td>All solid cancers, incidence</td>
<td>1.0 (0.3-1.9)</td>
</tr>
<tr>
<td>Preston 1994\textsuperscript{44}</td>
<td>Atomic bomb survivors</td>
<td>30.5 bone marrow</td>
<td>Non-CLL leukemia, mortality (N = 261)</td>
<td>1.4 (0.1-3.4)</td>
</tr>
<tr>
<td>Cardis 2007\textsuperscript{43}</td>
<td>15-country nuclear workers</td>
<td>15 mSv whole body</td>
<td>Non-CLL leukemia, mortality (N = 196)</td>
<td>1.93 (&lt; 0-7.14)</td>
</tr>
<tr>
<td>Muirhead 2009\textsuperscript{42}</td>
<td>NRRW radiation workers = 174,541</td>
<td>24.9 mSv whole body</td>
<td>Non-CLL leukemia, incidence (N = 177)</td>
<td>1.782 (0.17-4.36)</td>
</tr>
<tr>
<td>Krestinina 2005\textsuperscript{160}</td>
<td>Population radionuclide waste = 29,756</td>
<td>300 bone marrow</td>
<td>Non-CLL leukemia, incidence (N = 70)</td>
<td>4.9 (1.6-14.3)</td>
</tr>
<tr>
<td>Bithell &amp; Stewart 1975\textsuperscript{56}</td>
<td>OSCC case-control study of diagnostic in utero radiation and risk of pediatric cancers</td>
<td>Approximately 10 bone marrow</td>
<td>All leukemias, mortality (N = 4052)</td>
<td>RR = 1.49 (1.33-1.67)</td>
</tr>
<tr>
<td>Wakeford 2008\textsuperscript{18}</td>
<td>Meta-analysis of epidemiologic studies of diagnostic in utero radiation and pediatric leukemias; 32 studies excluding OSCC</td>
<td>Unknown</td>
<td>All leukemias, mortality and incidence</td>
<td>RR = 1.32 (1.19-1.46)</td>
</tr>
<tr>
<td>Preston 2007\textsuperscript{46}</td>
<td>Atomic bomb survivors = 105,427</td>
<td>30.8 breast</td>
<td>Breast cancer, incidence (N = 527)</td>
<td>0.87 (0.55-1.3)</td>
</tr>
<tr>
<td>Ostroumova 2008\textsuperscript{162}</td>
<td>Population radionuclide waste = 9908</td>
<td>40 stomach dose</td>
<td>Breast cancer, incidence (N = 131)</td>
<td>13.5 (2.5-27.8)</td>
</tr>
<tr>
<td>Ronckers 2008\textsuperscript{162}</td>
<td>Patients undergoing x-rays to monitor scoliosis</td>
<td>121 breast</td>
<td>Breast cancer, incidence (N = 78)</td>
<td>2.86 (0.07 to 8.62)</td>
</tr>
</tbody>
</table>

mGy indicates milligray; ERR, excess relative risk; Gy, gray; 95% CI, 95% confidence interval; NRRW, National Registry for Radiation Workers; non-CLL, leukemias other than chronic lymphocytic leukemia; mSv, millisieverts; OSCC, Oxford Survey of Childhood Cancers; RR, relative risk; TB, tuberculosis (patients underwent repeated fluoroscopic examinations to monitor lung collapse treatment).
treatment while limiting associated radiation exposures to levels as low as reasonably achievable. A few examples of the relevant literature base are provided, but the scope of this review precludes comprehensive assessment.

Evidence Justifying Selection of Imaging Procedures: Data Are Limited

**Justification: Evidence Basis**

In general, only limited data provide strong evidence to conclusively indicate who needs an imaging examination involving ionizing radiation instead of an alternative that does not expose the patient to ionizing radiation. Clearly, it is inappropriate to utilize an imaging test in lieu of obtaining a detailed medical history and a carefully performed physical examination (absent major trauma or a patient in extremis). The concept of the benefit/risk ratio should underlie justification decisions. If there is no difference in the expected benefit, the least invasive imaging tests (or those that do not require ionizing radiation) should be preferred over more invasive imaging tests (or those that do expose patients to ionizing radiation). An effort should also be made to avoid repeating the same examination for a given constellation or bout of symptoms and to consider the clinical urgency of the need for an imaging test (eg, ordering a test that can be performed immediately [often a CT]) versus another test, free of radiation-related risk, to be undertaken when an appointment is available (eg, ultrasound) or scheduled within a few days (eg, MRI, which does not involve ionizing radiation).

Because children and adolescents are at higher risk of developing radiation-associated cancers than older persons, there has been substantial debate about the optimal type of imaging tests for children and adolescents for certain indications (eg, CT scan vs ultrasound for suspected appendicitis). The recognition that children are at higher risk of developing cancer following exposure to radiation than adults has led to increasing reliance on clinical history and physical examination for children suspected of appendicitis and, only if necessary, the use of laboratory tests and imaging to confirm the diagnosis.

**Examples of Important Aspects of Justification**

Two examples illustrate important aspects of justification: 1) if higher dose imaging examinations are needed at all (eg, certain pediatric head trauma patients) or 2) if 2 or more higher dose imaging tests are needed at the same time (eg, posttreatment response in pediatric cancer patients). A third example, guidelines for breast cancer screening using mammography, illustrates some complexities associated with justification given knowledge gaps.

Head trauma is one of the most common reasons that a CT scan is ordered. While there is little argument that patients with a more severe head injury (eg, Glasgow coma score less than 13) will experience a greater benefit from a CT scan than any future radiation-related cancer risk, there is a substantial debate concerning routine CT for a child with a less severe injury (eg, Glasgow coma score greater than 14). In a prospective cohort study of 42,412 children presenting with Glasgow coma scale scores of 14 to 15, trained investigators recorded patient history, injury mechanism, and symptoms and signs before imaging results were known, and followed children to ascertain outcomes (including death, neurosurgery, intubation for more than 24 hours, or hospital admission of 2 nights or more). CT scans were obtained at the discretion of the emergency department clinician (n = 14,969 patients) and interpreted onsite (780 patients had traumatic brain injuries on CT scan). The investigators derived and validated age-specific prediction rules for clinically important traumatic brain injury. The prediction rules identified children at very low risk for whom the investigators concluded that CT scans were not required.

Patients with pediatric cancer are frequently treated with radiotherapy, depending upon the diagnosis and treatment protocol implemented. Regardless of the specific treatments, patients with pediatric cancer also undergo extensive imaging for diagnosis and clinical staging, treatment response assessment, and follow-up monitoring after treatment has ended. This assessment entails significant cumulative radiation doses. Developing an evidence-based approach to the diagnosis and ongoing monitoring of pediatric oncology patients is critical to limit cumulative radiation dose, but there is extensive debate. Although it is clear that CT or PET/CT scans are valuable for diagnostic purposes and during the early stages of treatment, it may not be necessary to obtain diagnostic contrast-enhanced CT at the same time as PET imaging. As noted earlier, it is particularly important to consider alternative imaging procedures for cancer patients who are at high risk of developing radiation-related second malignancies. The high incidence of radiation-related second tumors in patients with hereditary Rb has led pediatric ophthalmologists and pediatric radiologists to propose guidelines that call for the use of MRI rather than CT in such patients.

Strong evidence from randomized trials has shown that screening mammography from ages 40 to 69 years reduces mortality from breast cancer. There are differing interpretations of the evidence and some differences among the guidelines with regard to screening intervals and ages at which to start and stop screening. Nevertheless, there is good agreement about screening for women ages 50 to 74 years. Reasons for the differences are mostly due to the absence of data from multiple large randomized trials to address the following knowledge gaps: lack of accurate and reproducible measures of the sensitivity of mammography screening for the identification of breast cancer, particularly in
those with dense breast tissue; and insufficient evidence about the benefits versus harms of screening mammography in older women (aged 75 years and older), annual versus biennial screening, and overdiagnosis (eg, limited knowledge about which ductal carcinomas in situ will go on to become invasive and the rapidity of spread of invasive breast cancers). Given these gaps, the screening guidelines that have been proposed are based on expert consensus informed by critical assessment of the literature or on statistical modeling. The estimated radiation dose associated with a single view in mammography is presently about 2 mGy. As indicated above, the risk of radiation-induced breast cancer from routine mammographic screening of women ages 50 to 74 years is small compared with the expected mortality reduction from screening in the general population, but the benefit may not outweigh the risk of screening female BRCA mutation carriers younger than age 35 years.

Optimization of Radiation Dose

Need for Protocols Tailored to Patient Characteristics

Once the decision has been made that a CT scan is appropriate, the radiological medical practitioner must tailor the CT parameters (milliamperes, kilovoltage peak, automatic exposure control, and others) and protocol (cover only the anatomic region necessary) to the patient's size and age. There should be as few phases as possible (usually one) as each run (without contrast, with contrast, delayed) multiplies the dose. These considerations should be applied to all patients, but young children, pregnant women, and obese patients require further protocol modifications to optimize dose. Technological improvements, including automatic tube current modulation (which modifies the dose depending on the thickness of the anatomic site to be examined) and noise reduction filters, will reduce further the doses from CT while continuing to improve images.

It is important to include the dose report on all CT and other radiation-producing diagnostic procedures. As the dose cannot be determined by the appearance of the images, this is the only way to verify that the correct protocol was used. For CT, the current metric is the volume-weighted CT dose (CTDIvol). In the future, better metrics, such as size-specific dose estimates CTDIvol as advocated by the American Association of Physicists in Medicine, will hopefully become the norm.

Example of Successful Dose Reduction

A prospective, controlled, nonrandomized study enrolled 4995 sequential patients undergoing cardiac CT angiography (CCTA) at 15 hospital imaging centers during a 2-month control period, followed by an 8-month intervention period using a best-practice CCTA scan model (including minimized scan range, heart rate reduction, electrocardiographic-gated tube current modulation, and reduced tube voltage), and then a 2-month follow-up period. Compared with the initial control period, patients' estimated effective dose was reduced from 21 mSv to 10 mSv, with the most notable reduction in dose occurring at low-volume sites.

Diagnostic Reference Levels

In 1990, the metric of normative values for patient radiation dose from a given procedure was introduced in the United Kingdom and was subsequently recommended by the ICRP. These normative measures, designated “diagnostic reference levels,” typically correspond to the 75th percentile of the distribution of measured dose values for particular imaging procedures. Diagnostic reference levels serve as benchmarks for comparing dose levels for imaging tests at a given facility with the broad range of dose levels from many other institutions. Such benchmarks should be regularly evaluated and, if exceeded, addressed by medical physicists and radiological medical practitioners, as part of a facility's quality assurance program in radiation protection. These benchmarks should be periodically reevaluated and reduced, as current practices will certainly lower the 75th percentile dose.

Appropriateness Criteria and Evidence-Based Radiology

History

The observation of striking regional (including small area) variation in the use of medical procedures and debate about overuse, underuse, and the “right” level of use led to the concept of “appropriateness of medical procedures.” This concept was defined to mean that the expected health benefits from procedures should exceed by a sufficiently wide margin the expected negative consequences of performing the procedures. The RAND Corporation and the University of California at Los Angeles operationalized the concept of appropriateness of a specific medical procedure for specific indications by basing it on a quantitative score provided by expert panels (drawn from multiple medical specialties and including physicians who did and those who did not perform the procedure) that were guided by formal literature review. Each specific procedure/indication for use category was established for a homogeneous group of patients meeting the criteria for appropriateness; there could be many specific indications for a given procedure. A rigorous, reproducible statistical technique was used to obtain a consensus score on an ordinal scale. The approach has demonstrated good reliability, validity, and predictive power, and has confirmed the efficiency of the method for estimating the appropriateness of a variety of specific procedures for medical care. Randomized trials comparing general guidelines with specific appropriateness criteria in
decisions about diagnostic testing have found that appropriateness criteria were effective in achieving more appropriate test ordering.\textsuperscript{205}

**Description of ACR Appropriateness Criteria**

In 1993, the ACR developed the scientific-based ACR Appropriateness Criteria to guide decisions about ordering imaging procedures. These guidelines are comprehensive, currently address more than 175 topics with over 850 variants, are produced through consensus of panels of recognized experts, are updated regularly, and incorporate medical practice guidelines used by the Agency for Healthcare Research and Quality as designed by the Institute of Medicine. The approach relies not only on evidence-based assessment of the scientific evidence but also on expert consensus when data from scientific outcome and technology assessment studies are insufficient.\textsuperscript{206}

**Limitations**

The ACR Appropriateness Criteria have been criticized for not utilizing the rigorous methodology of the evidence-based medicine approach for radiology.\textsuperscript{207} Although there is support for the development of a systematic evidence-based approach to evaluate each specific radiologic procedure/indication, it is acknowledged that there is a lack of even limited measures, such as sensitivity and specificity for certain procedures, let alone more rigorous types of evaluation such as randomized trials. These major limitations, in conjunction with the rapid adoption and use of new imaging technologies, limit more comprehensive use of evidence-based approaches.\textsuperscript{208,209} Similar limitations apply to the Appropriate Use Criteria for Cardiac Computed Tomography developed by the ACC and other collaborating organizations. Studies have identified large proportions of clinical indications for which matching clinical fields or variants cannot be identified in the ACR or ACC Appropriateness Criteria.\textsuperscript{210,211} Another major problem is the low utilization of the ACR and perhaps the ACC appropriateness criteria, likely due to a lack of awareness of these resources.\textsuperscript{212}

**Examples Illustrating Important Aspects of Appropriateness Criteria**

To evaluate a child with a first nonfebrile seizure (which occurs in 1%–2% of children and is generally idiopathic), unless a child is at high risk (eg, the presence of a predisposing condition), an emergent CT is not indicated and well-appearing children who meet low-risk criteria can be discharged if follow-up is assured.\textsuperscript{213} For low-risk children, an evidence-based assessment demonstrates that MRI is a sensitive neuroimaging modality that can detect neurodevelopmental lesions (eg, heterotopic gray matter, cortical dysplasia, and polymicrogyria, among others), some of which may be difficult to detect on CT.\textsuperscript{214,215} Since many of the causes of seizures are not seen as well or at all on CT, the use of CT exposes children to risk without adequate benefit. That is, CT in these children is not justified. Similarly, for a child with new onset of headaches, the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society have concluded that routine neuroimaging is not indicated for children with recurrent headaches and a normal neurologic examination.\textsuperscript{216} Neuroimaging evaluation is justified in children with an abnormal neurologic examination or other physical findings or symptoms that may suggest disease of the central nervous system. MRI in this situation will provide more information without radiation exposure compared with CT.

**Studies Reporting Inappropriate Ordering of CT Examinations**

Evaluation of data from the National Hospital Ambulatory Medical Care Survey (1998–2007) provides indirect evidence of inappropriate ordering of CT or MRI examinations in emergency department visits. These data revealed that there was no change during the period in the prevalence of patients admitted to the hospital or intensive care unit from emergency departments, whereas the prevalence of CT or MRI use in the emergency departments increased from 6% to 15%.\textsuperscript{217} Review of data to assess the use of screening cervical CT examinations performed after trauma revealed that close to 24% of the CT scans of patients that were negative for an acute injury had no written documentation of any of the 5 criteria established by the National Emergency X-Radiography Utilization Study to identify patients with a low probability of cervical spine injury who do not require cervical spine imaging.\textsuperscript{218} Retrospective review of the medical records from 459 outpatient CT and MRI examinations from primary care physicians in the state of Washington using appropriateness criteria from a radiology benefit management company similar to the ACR Appropriateness Criteria revealed that 74% of the imaging examinations were considered appropriate, while 26% were not considered appropriate (examples of the latter included brain CT for chronic headache, lumbar spine MRI for acute back pain, knee or shoulder MRI in patients with osteoarthritis, and CT for hematuria during a urinary tract infection).\textsuperscript{219} The investigators followed up the results of the examinations and found that 58% of the appropriate studies but only 24% of the inappropriate studies had positive results and affected subsequent management.

**Alternatives and Enhancements of the Appropriateness Criteria**

For some patients with chronic remitting and relapsing disorders, such as Crohn disease, who may require multiple imaging examinations, evaluation of appropriateness criteria may be less important than consideration of
alternate imaging procedures that provide the data for clinical decision-making while reducing radiation-related risks.\textsuperscript{220} Despite the ACR Appropriateness Criteria, the continuing increase in imaging has led to consideration of preauthorization programs based on Appropriateness Criteria. Utilization patterns of CT and MRI before and after implementation of an Israeli managed care preauthorization program, based on the ACR Appropriateness Criteria and the UK Royal College of Radiology guidelines, demonstrated that annual performance rates of CT and MRI decreased from 25.9 and 7 examinations, respectively, per 1000 in the year 2000 to 17.3 and 5.6 examinations, respectively, per 1000 in 2003, representing reductions of 33\% for CT and 9\% for MRI.\textsuperscript{221} Decision support software that uses the ACR Appropriateness Criteria has been built into a computerized radiology examination ordering system, making it available at the time the imaging study is requested.\textsuperscript{222,223} This method has been shown to be effective in decreasing the rate of imaging utilization.\textsuperscript{223} It is also essential for reports of all CT and other radiologic examinations to be incorporated into medical records immediately to reduce the frequency of repetition of the same or similar diagnostic radiologic procedures.

Other Strategies to Reduce Radiation Doses From Diagnostic Examinations

\textbf{Radiation Safety Alliances and Campaigns by Professional Organizations}

The Society for Pediatric Radiology sponsored the first ALARA conference on CT dose reduction in 2001, bringing together physicists; radiation biologists; manufacturers; and members of the US Food and Drug Administration (FDA), the National Cancer Institute, and the National Council on Radiation Protection and Measurements with referring and radiologic practitioners. The Society has continued to sponsor biennial conferences focusing on various topics to limit unnecessary procedures and decrease radiation doses from CT.\textsuperscript{224-227} A crucial offshoot of these efforts was the formation of the Alliance for Radiation Safety in Pediatric Imaging in 2007. By 2008, this advocacy group was formalized with the founding organizations including the Society for Pediatric Radiology, the American Society of Radiologic Technologists, the ACR, and the American Association of Physicists in Medicine. This coalition of professional health care organizations joined with manufacturers of imaging equipment to work together for both appropriate imaging and for reducing the radiation dose from imaging procedures. The organization has continued to grow and now includes more than 65 organizations committed to reducing radiation dose.\textsuperscript{228,229} The Image Gently campaign is an initiative of this organization (available at: www.imagegently.org).

The Society for Pediatric Radiology has a program to expose second- and third-year medical students to information about imaging and radiation-producing tests. The Society is also working with the nationwide Children’s Oncology Group to devise dose-reducing protocols for the diagnosis, treatment, and surveillance of patients with pediatric cancers.

The ACR, the Radiological Society of North America, the American Association of Physicists in Medicine, and the American Society of Radiologic Technologists have collaborated with the Image Gently campaign of the Alliance for Radiation Safety in Pediatric Imaging to create the Image Wisely campaign, whose objectives are to apply the same principles of appropriate and lower radiation doses to diagnostic procedures undertaken in adults.

\textbf{Summit of 60 Organizations to Discuss Causes and Effects of Overutilization of Imaging}

A 2009 summit cosponsored by the American Board of Radiology Foundation, the National Institute of Biomedical Imaging and Bioengineering, and the American Board of Radiology identified several contributors to overutilization, including the payment system and reimbursement of procedures on a procedure basis; little control over the number of imaging devices available in populations of patients; high reimbursement for imaging procedures encouraging nonradiologists to add imaging to services provided to patients; little legislative or regulatory action to control inappropriate, financially motivated self-referral practices that have led to higher utilization\textsuperscript{230}; defensive medicine practices (43\% of 824 physicians completing a survey on defensive medicine reported using imaging technology in clinically unnecessary circumstances\textsuperscript{231} and 28\% of CT scans were ordered primarily for defensive purposes in one state\textsuperscript{232}); lack of education of referring medical practitioners from medical school through residency training, practice, and continuing medical education at meetings; failure to educate referring medical practitioners when inappropriate tests are ordered; failure of radiologists to review imaging requests for appropriateness; failure to educate patients who demand imaging tests about benefits and risks; and inadvertent or deliberate duplication of imaging studies (20\% of all patients surveyed in 2007 had duplicate imaging examinations).\textsuperscript{233,234} Areas for improvement identified by summit participants included better education and training of referring medical practitioners, a national collaborative effort to develop comprehensive evidence-based appropriateness criteria for imaging, greater use of practice guidelines in requesting and conducting imaging studies, decision support at the point of care, education of patients and the public,\textsuperscript{235} accreditation of imaging facilities, management of self-referral and defensive medicine
by the physician community acting in concert or by legislative action to place restrictions on self-referral, and payment reform.234

**FDA Center for Devices and Radiological Health Initiative to Reduce Unnecessary Radiation Exposure From Medical Imaging**

In February 2010 the FDA launched an Initiative to Reduce Unnecessary Radiation Exposure. The overarching goals are to promote the safe use of medical imaging devices, support informed clinical decision-making, and increase patient awareness. To promote the safe use of medical imaging devices, the FDA will establish requirements for manufacturers of CT and fluoroscopic devices to incorporate additional safeguards into equipment design, labeling, and user training; partner with the Centers for Medicare and Medicaid Services to incorporate key quality assurance practices into accreditation and participation criteria for imaging facilities and hospitals; and recommend that the health care professional community, in collaboration with the FDA, continue efforts to develop diagnostic reference levels for CT, fluoroscopy, and nuclear medicine procedures locally and also through a national radiation dose registry. To support informed clinical decision-making, the FDA will establish requirements for manufacturers of CT and fluoroscopic devices to record radiation dose information for use in patient medical records or a radiation dose registry and will recommend that the health care community continue to develop and adopt criteria for the appropriate use of CT, fluoroscopy, and nuclear medicine procedures that use these techniques. To increase patient awareness, the FDA will provide patients with tools to track their personal medical imaging history.

**Summary of Strategies for Reducing Radiation Exposure from Diagnostic Imaging Procedures**

Professionals and professional organizations that play a key role in the appropriate utilization of medical imaging are the referring medical practitioners who are responsible for ensuring that a diagnostic procedure involving ionizing radiation is necessary for a patient’s care and should be expected to do more good than harm (designated as justification) and the radiological medical practitioners who, together with qualified medical physicists and manufacturers of x-ray equipment, provide images adequate for diagnosis and treatment while keeping the radiation dose at levels as low as reasonably achievable (designated as optimization). Only limited data provide strong evidence about which categories of patients should be evaluated with an imaging examination involving ionizing radiation instead of an alternative. Approaches for optimizing doses from imaging procedures have undergone limited assessment. Diagnostic reference levels (corresponding to the 75th percentile of the distribution of doses from all such examinations) provide normative values and serve as benchmarks for comparing dose levels and for investigating imaging practices if these levels are exceeded. The history, methodology, and limitations of the ACR Appropriateness Criteria program to guide decisions about ordering imaging procedures are described. Growing evidence provides documentation that a substantial proportion of imaging examinations are inappropriately ordered and performed. Imaging examinations that do not require ionizing radiation should be preferred, when appropriate, for patients with chronic disorders who require repeated imaging for diagnostic and treatment purposes. Strategies that can reduce unnecessary imaging examinations include preauthorization and the use of decision support software. Finally, efforts to reduce radiation doses from diagnostic procedures include those by radiation safety alliances of radiologists, physicists, radiobiologists, clinicians, and manufacturers; a summit of 60 organizations to discuss the causes and effects of overutilization of imaging and to identify areas for improvement; and the FDA Center for Devices and Radiological Health Initiative to promote the safe use of medical imaging devices, support informed clinical decision-making, and increase patient awareness of radiation exposures from medical imaging.

**Recommendations for Clinicians**

1. Become knowledgeable about the radiation doses for the imaging studies.
2. Consider ultrasound and MRI when these are appropriate alternatives since these procedures do not subject the patient to ionizing radiation.172,236
3. Do not order a higher radiation dose study if a lower dose study (or an imaging study that does not use ionizing radiation) can provide the clinical information needed.
4. All requests for imaging studies should be justified (eg, when all benefits and risks are considered, the study should be expected to do more good than harm).
5. Available aids for justification, such as the ACR’s Appropriateness Criteria and the ACC’s Appropriate Use Criteria for Cardiac Computed Tomography, should be utilized to provide guidance for choosing the most appropriate imaging examination.
6. Unnecessary imaging studies (duplicate studies and those that are not medically necessary) should not be performed.
7. In general, neither screening nor elective x-ray examinations should be performed on pregnant women.
8. Refer patients who require imaging studies to a facility that strives to optimize radiation dose, so that imaging is performed with the least amount of radiation necessary to provide adequate image quality.
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