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STATE-OF-THE-ART PAPER

Effects of Radiation Exposure From Cardiac Imaging

How Good Are the Data?

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Concerns about medical exposure to ionizing radiation have become heightened in recent years as a result of rapid growth in procedure volumes and the high radiation doses incurred from some procedures. This paper summarizes the evidence base undergirding concerns about radiation exposure in cardiac imaging. After classifying radiation effects, explaining terminology used to quantify the radiation received by patients, and describing typical doses from cardiac imaging procedures, this paper will address the major epidemiological studies having bearing on radiation effects at doses comparable to those received by patients undergoing cardiac imaging. These include studies of atomic bomb survivors, nuclear industry workers, and children exposed in utero to x-rays, all of which have evidenced increased cancer risks at low doses. Additional higher-dose epidemiological studies of cohorts exposed to radiation in the context of medical treatment are described and found to be generally compatible with these cardiac dose–level studies, albeit with exceptions. Using risk projection models developed by the U.S. National Academies that incorporate these data and reflect several evidence-based assumptions, cancer risk from cardiac imaging can be estimated and compared with the benefits from imaging. Several ongoing epidemiological studies will provide better understanding of radiation-associated cancer risks.
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In recent years, intensive efforts have been initiated to reduce the ionizing radiation associated with cardiac imaging. It is now routine for publications addressing cardiac imaging to report radiation doses, and several studies have estimated cancer risks from a variety of cardiac imaging procedures. Concern about potential deleterious effects from radiation, specifically cancers, abounds, in some cases even leading to avoidance of essential procedures. As many practitioners are unfamiliar with the terrain of the epidemiological evidence base undergirding these concerns about radiation, this paper attempts to provide a tour of this landscape.

It is important for a discussion of the downside of cardiac imaging to put these risks in context. Risks from testing should not be viewed in isolation, but rather within the context of a sober and simultaneous evaluation of the benefits, risks, and costs of a given test in a specific clinical context. Specifically, although imaging has its risks, it also has indubitable benefits, in terms of improved diagnosis and prognosis, the ability to affect medical therapy and provide guidance for interventions, and ultimately improve patient and societal outcomes. Although strong evidence for the latter, which is the most important (1), has been the slowest and most difficult to accumulate, we do have examples of studies demonstrating that management strategies incorporating imaging can improve patient-important outcomes (2), and in an environment in which we are keenly aware of potential risks and limits on resources, impact on outcomes is increasingly recognized as the level of imaging evidence desired.

Reasons for the concern about ionizing radiation in cardiology. Why has ionizing radiation become a concern in cardiology? I would posit that the reason is 2-fold. First, procedure volumes have grown tremendously. Figure 1 illustrates the growth in nuclear single-photon emission computed tomography myocardial perfusion imaging volume, which increased by nearly 3-fold over the course of a decade (3). Although information on cardiac computed tomography (CT) volume is not as robust, the number of coronary CT angiograms increased from virtually zero in the early 2000s to several hundred thousand studies per year.

A second reason for the increasing concern is the magnitude of the doses of radiation that many patients undergoing cardiac imaging procedures have received and continue to receive (Table 1). It is easy for patients undergoing a single cardiac imaging examination to receive the amount of radiation equivalent to 1,000 chest x-rays, a lifetime of screening mammograms, or many years' background radiation.

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Abbreviations and Acronyms

BEIR = Biological Effects of Ionizing Radiation
CT = computed tomography
ERR = excess relative risk
LNT = Linear No-Threshold
MI = myocardial infarction

If one takes dramatically increased volumes and multiplies them by high doses, the net result is a public health problem. The National Council on Radiation Protection and Measurements, a congressionally chartered organization aimed at ensuring the radiation safety of the U.S. public, has performed comprehensive reviews of radiation exposure to the American population from all sources twice over the past 3 decades, once covering the period 1980 to 1982 (4), and once for 2006 (5). The difference between these 2 reports is striking (Fig. 2). In the earlier time period, nonmedical radiation constituted a per capita effective dose of 3 mSv per year, whereas medical radiation accounted for 0.53 mSv per year. Although nonmedical radiation exposure remained basically constant over the 25-year period, medical radiation increased about 6-fold, to 3.0 mSv per capita per year. Of note, radiation from cardiac imaging and intervention accounted for roughly 17% of all ionizing radiation to the American public from all sources (excluding radiotherapy).

Types of radiation effects. Two fundamental terms are used to classify types of effects from radiation: *deterministic effects* and *stochastic effects* (6). Deterministic effects, also called tissue reactions, are those due to injury of a population of cells from radiation-induced cell death or serious malfunction. Deterministic effects characteristically only occur above a threshold dose, which, although varying from individual to individual, is high, often only after a large proportion of cells in a tissue have been killed by radiation. The severity of deterministic effects commonly increases with dose, as more cells are killed or damaged. Examples of deterministic effects are skin and hair changes (7), cardiovascular disease, and cataracts. Deterministic effects typically do not occur at the levels of radiation that patients undergoing noninvasive imaging procedures receive, although there have been some widely reported examples of patients undergoing CT angiography/perfusion studies of the brain who received high doses causing hair loss (8).

In contrast, stochastic effects, which are the effects of concern from imaging tests, are those for which the probability of an effect, but not its severity, depend on dose of radiation received (6). Stochastic effects are generally caused by radiation-induced mutations rather than by cell death.

Table 1 Typical Effective Doses of Some Sources of Radiation

Source	Typical Dose (mSv)	Chest X-Rays (Posteroanterior)
Chest x-ray (posteroanterior)	0.02	1
Chest x-ray (posteroanterior and lateral)	0.10	5
Round trip flight, New York to New Orleans	0.02	1
Backscatter scanner for airport screening	0.001	1/20
Mammogram	0.7	35
Head CT	2	100
Background radiation to public (annual)	3	150
Abdominal CT	10	500
Average annual occupational dose limit* (ICRP) (6)	20	1,000
Dual isotope MPI or helical coronary CTA	25	1,250
Highest doses received by Fukushima workers	250	12,500

*Average over 5-year period. Allows for up to 50 mSv in any single year.
CT = computed tomography; CTA = computed tomography angiogram; ICRP = International Commission on Radiological Protection; MPI = myocardial perfusion imaging.

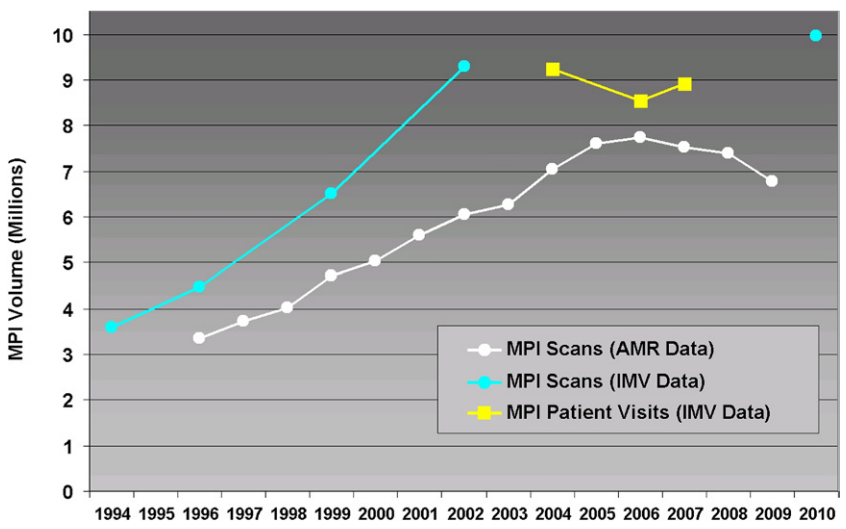

Figure 1 Growth in Nuclear Single-Photon Emission Computed Tomography MPI Volume

Data sources: Arlington Medical Resources (AMR), courtesy Greg Thomas, MD, and IMV Medical Division, e.g. (3).
MPI = myocardial perfusion imaging.

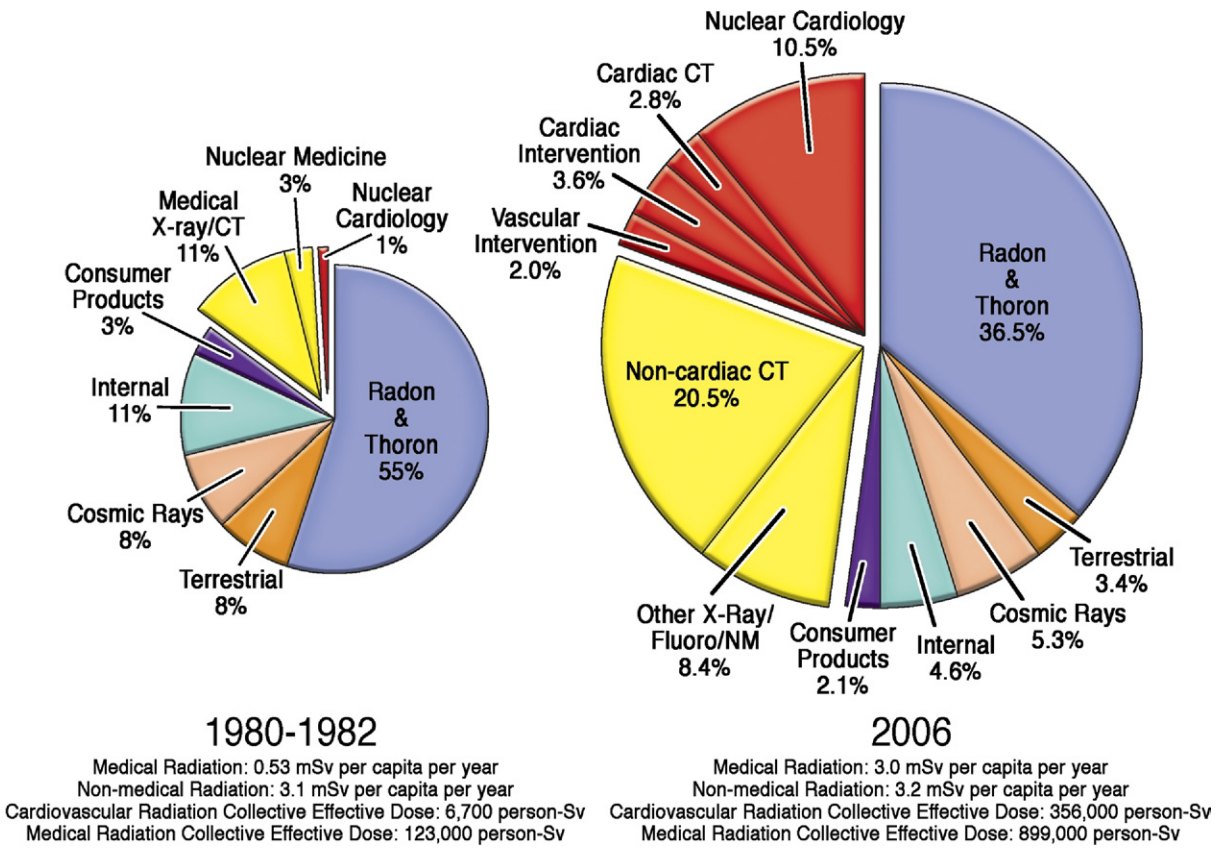

Figure 2 **The Increasing U.S. Radiation Burden**

Data from National Council on Radiation Protection and Measurements Reports 93 (4) and 160 (5), from all medical sources except radiation therapy. Note that collective dose from cardiovascular imaging and intervention in 2006 constituted 19% of the collective effective dose of radiation from all nonradiotherapy sources to the U.S. population, and was nearly 3 times the collective dose from all medical sources in the early 1980s. CT = computed tomography; Fluoro = fluoroscopy; NM = nuclear medicine.

The term *stochastic* itself means probabilistic, and stochastic effects do not definitely occur at a specific dose but rather occur with a probability that is generally thought to increase as dose increases. Severity of a stochastic effect does not depend on the radiation dose—the mutation occurs or it does not. The 2 common types of stochastic effects are malignancies and heritable disease in offspring. Cancers occur after a latency period, which evidence suggests is at least 5 to 10 years for most solid tumors and 2 years for nonchronic lymphocytic leukemia leukemias (radiation is not thought to cause chronic lymphocytic leukemia) (9). Although there are significant experimental data for heritable effects of radiation, there is no direct evidence in humans (6).

How ionizing radiation is quantified. Two classes of terms are used to numerically characterize ionizing radiation: *doses* and *risks*. A dose is a measure of energy deposition in matter, whereas a risk is the probability of a deleterious event, for example, cancer incidence or mortality, occurring. A slew of different types of dose-related quantities exist, resulting in quantification that can often be ambiguous and confusing. Doses to individual organs are typically reported as the concentration of energy deposited per unit of matter (organ absorbed doses), and reported in units of milligrays (mGy), a special unit term denoting millijoules per kilogram of tissue in this context. There are several modality-specific dose indices, such as the dose-length product for CT and the kerma-area product for fluoroscopy (10).

In the past few years, the type of dose reported most commonly in the context of medical imaging is the effective dose, a doubly weighted measure of organ absorbed doses, weighted to reflect the type(s) of energy and the relative radiosensitivities of each organ/tissue, summed over all organs (6). Effective dose is typically reported using another special unit, the millisievert (mSv), which also denotes millijoules per kilogram of tissue, and is commonly estimated in cardiac imaging by multiplying a modality-specific dose index by a standard conversion ("*k*") factor (11). However, since organ doses used in the definition of effective dose are those in a nonobese, gender-averaged "reference person," and tissue weighting factors are rounded values reflecting multiple factors such as radiation-related risk and lethality of cancer and effect on quality of life,

averaged over both genders and all adult ages, effective dose is not a measure that is designed to characterize radiation exposure to an individual patient from an individual study. Rather, it is designed to approximately characterize the radiation burden to a typical individual from a given procedure and protocol. As such, although widely done in the literature, it is "off-label" and formally improper to refer to the effective dose from a specific study performed on a specific patient.

Radiation dose to cardiac imaging patients. Typical effective doses from cardiac imaging studies are illustrated in Figure 3 (12). Such point estimates, however, fail to reflect the tremendous variability, between sites and between studies at a given site, that exists in dose indices for a given procedure (13). For example, in the PROTECTION I (Prospective Multicenter Study on Radiation Dose Estimates of Cardiac CT Angiography in Daily Practice I) study evaluating radiation dose from 50 sites worldwide, site-specific median dose–length products ranged 7-fold, and were over 2,000 mGy·cm, corresponding to a median effective dose of at least 30 mSv, in the highest-dose sites (14). Even using state-of-the-art technology that permits "sub-millisievert" scanning, some patients may still receive substantial amounts of radiation (Fig. 4) (15). In nuclear cardiology, dual isotope protocols may be associated with effective doses typically over 25 mSv. Moreover, many patients undergoing a single cardiac imaging study will undergo many procedures involving ionizing radiation. In 1 series of 1,097 patients undergoing index myocardial perfusion imaging, the typical patient underwent a median of 14 additional procedures involving ionizing radiation over a 20-year period, thereby receiving a cumulative estimated effective dose of 64 mSv (16).

Evidence of cancer risk at levels of radiation commonly received by cardiac imaging patients. Thus, effective doses from cardiac imaging procedures on the order of up to 50 mSv are not uncommon in selected patient populations. In evaluating epidemiological data relating ionizing radiation exposure to cancer risk for generalization to populations of patients exposed to cardiac imaging procedures, the ideal study would be characterized by a number of features. It would involve exposure of primarily adult patients, who constitute the bulk of cardiac imaging patients, to very-low-dose (<50 mSv) x-rays or gamma-rays from an acute, not chronic, medical exposure. The ideal study would be a cohort study, rather than a case-control study, for which there may be susceptibility to recall bias and an inability to adjust for all confounders, and have adequate statistical power to detect an increase in cancer incidence in the exposed cohort. A real challenge is posed by this latter consideration, since radiation is a weak carcinogen, and background cancer rates in the population are so high (lifetime risk of approximately 42% [9]). The National Academies (17) have estimated the sample size required to detect a significant increase in cancer mortality in a cohort exposed to a specific dose of radiation to an organ. For doses between 5 and 50 mGy, these figures range between about 100,000 and 10 million (Fig. 5 [18]). The cost of performing such a study, with long follow-up, is very high, and as such there are very limited data from such low-dose cohorts. The 3 major very-low-dose epidemiological studies have evaluated Japanese atomic bomb survivors, nuclear industry workers, and children exposed to x-rays in utero. None involves exposure to cardiac imaging procedures or to adult medical imaging procedures, and none meets all of the characteristics of the ideal study, but their results uniformly, and statistically significantly, suggest an increase in cancer risk at radiation doses commonly received by cardiac imaging patients (Table 2).

VERY-LOW-DOSE STUDIES. The Life Span Study (LSS) represents an extensive undertaking on the part of the Japanese Ministry of Health, Labor, and Welfare and the U.S. Department of Energy and National Academy of

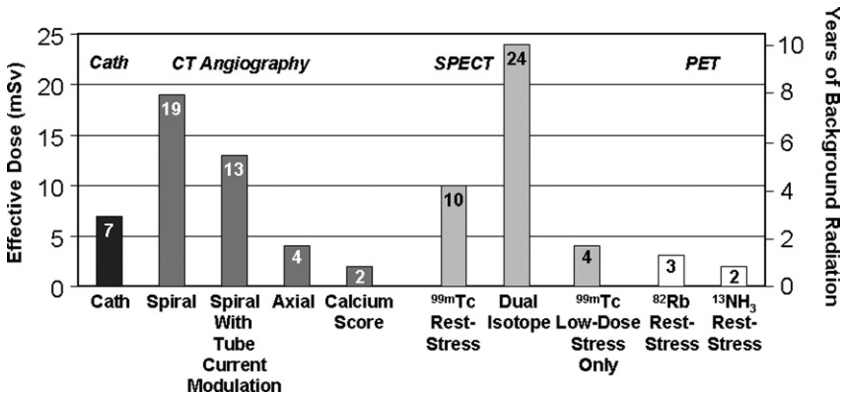

Figure 3 Typical Effective Doses From Cardiac Imaging Procedures

Adapted from Einstein (12) with permission from BMJ Publishing Group Ltd. PET = positron emission tomography; other abbreviations as in Figures 1 and 2.

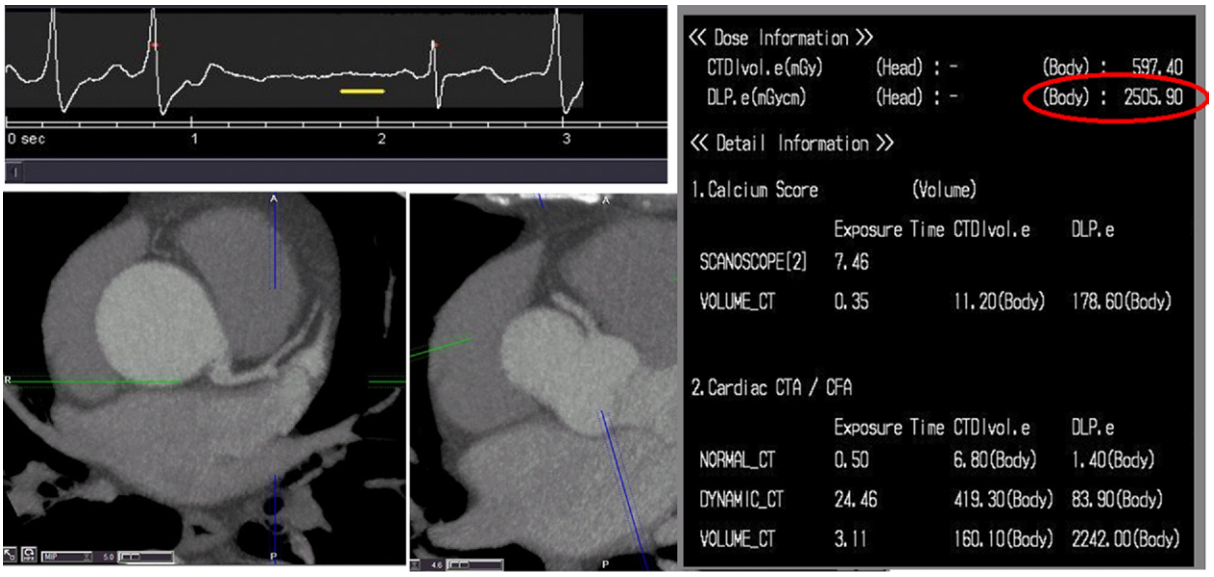

Figure 4 **Coronary CT Angiogram Performed in a 64-Year-Old Obese Man With Atypical Chest Pain and Frequent Ventricular Ectopy**

The scanner used is most commonly operated using a tube voltage of 100 kVp and single-heartbeat volume scanning with x-rays delivered only during a ~400-ms window during diastole, resulting in a dose-length product (DLP) for angiography of ~60 to 150 mGy·cm. Here, because of the patient's habitus and ectopy, the scanner was operated at 120 kVp and a scan mode that leaves the x-ray tube on throughout the cardiac cycle and continues image acquisition in subsequent beats if ectopy is detected. The study was diagnostic and excluded coronary artery disease **(bottom left)**, despite 3 out of 4 heartbeats being premature ventricular contractions **(top left)**; however the x-ray tube remained on for over 3 s, and the total DLP was ~2,500 mGy·cm **(top right)**. In a population of patients undergoing similar scans, this would correspond to an estimated effective dose of ~78 mSv using an updated conversion factor (15).

Sciences, designed to understand the relationship between radiation exposure and cancer risk in survivors of the atomic bombings in Hiroshima and Nagasaki. It is one of the few radiation effects studies comprised of a basically healthy population of both genders and all ages exposed to a wide range of radiation doses, and presently has analyzed over 40 years of follow-up data to assess risks of radiation-attributable cancer incidence (19). Survivor-specific dosimetry estimates have been refined multiple times, and reflect numerous factors, including distance from the hypocenter, information on acute effects, such as burns and epilation, and shielding history, including detailed information on location, position, and surroundings at the time of the

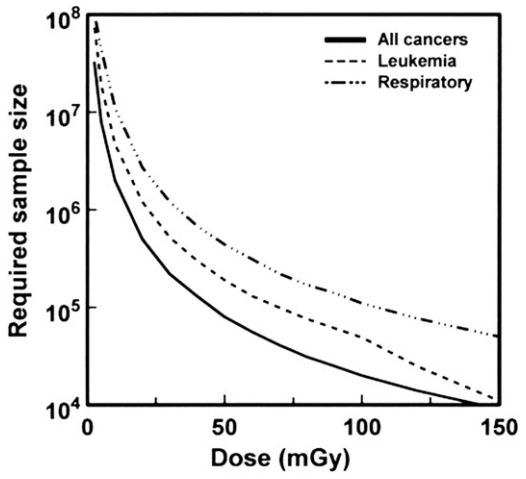

Figure 5 **Sample Size of a Cohort That Would Be Required to Detect a Significant Increase in Cancer Mortality in That Cohort**

Data show exposure to different radiation doses and assume lifetime follow-up. Reproduced with permission from Brenner et al. (18), based on National Research Council 1995 (17). Copyright 2003 National Academy of Sciences, U.S.A.

Table 2 **Characteristics of Epidemiological Studies Addressing Cancer Risk Associated With Very-Low-Dose (<50 mSv) Ionizing Radiation**

Population	Atomic Bomb Survivors	Nuclear Workers	In Utero X-Ray
Primary study	Life Span Study	15-Country Study	Oxford Survey of Childhood Cancer
Study characteristics			
Adults	✓	✓	
Medical			✓
X-ray or gamma-ray only			✓
<50 mSv	✓	✓	✓
Acute exposure	✓		✓
Cohort study	✓	✓	
Adequate power	✓	✓	✓
Sample size	120,321	407,391	30,552
Typical dose (mSv/mGy)	29	19.4	~10
Excess relative risk of cancer*	0.02	0.02	0.39

All excess relative risks are statistically significant. *At typical dose.

bombing (20). Analysis of LSS data divided Hiroshima and Nagasaki residents into "exposed" and "nonexposed" cohorts, depending on whether radiation dose to the colon was >5 or <5 mGy (comparable to 5 mSv effective dose since exposure was basically uniform throughout survivors' bodies and most exposure was from gamma-rays). Among the subset of the exposed cohort alive without cancer on January 1, 1958, and with doses of no more than 100 mSv, constituting 27,789 individuals typically between 2,000 and 3,000 yards of the hypocenter, mean dose was 29 mSv, and 4,406 solid cancers were observed between 1958 and 1998 (Fig. 6). The number of solid cancers expected, based on rates in the nonexposed cohort, was 4,325, and thus there were 81 (2%) excess cancers attributed to radiation, that is, an excess relative risk (ERR) of 0.02 (19). Rates of excess common cancers were 2.0% for colon, 1.3% for liver, 2.3% for lung, 4.3% for female breast, 1.8% for ovary, 0.4% for prostate, 3.1% for bladder, 0.4% for kidney, 3.9% for thyroid, and 1.9% for nervous system including brain.

The 15-Country Study of Cancer Risk in Radiation Workers in the Nuclear Industry (21,22) involved 5.2 million person-years of follow-up of workers at 154 facilities, 90% of whom received facility- or national registry-recorded doses of <50 mSv from chronic occupational exposure. A total of 24,158 workers died during follow-up, including 196 from leukemia and 6,519 from all other cancers, for which ERR was 0.97 cancers/Sv (95% confidence interval: 0.14 to 1.97). Testing for heterogeneity provided no evidence for differences in risk between cohorts, countries, or groups of facilities, although the point estimate for ERR was highest for Canada and when Canadian workers were excluded, ERR was no longer significantly different from 0 (0.58, −0.22 to 1.55). Risk estimates increased with increasing lag period, from 0.76 (0.07 to 1.59) with 5-year lag to 1.68 (0.22 to 3.48) with 20-year lag. One limitation of this study is that data were not available to adjust directly for possible confounders due to smoking, diet, and occupational exposures, although these were partially addressed indirectly by adjustment for socioeconomic status. ERR estimates were higher than, but statistically compatible with, those from the Life Span Study, which excluded survivors dying or developing cancer in the first 13 years between 1945 and 1958; however, these elevated ERR estimates have been observed to be sensitive to the impact of missing dosimetry at 1 Canadian facility. Methodological concerns such as the incomplete dosimetry data, possible confounders, and inclusion criteria selected have engendered controversy about the 15-Country Study's findings and interpretation (23).

The third large population evaluated after very-low-dose radiation exposure is children exposed to x-rays in utero. The largest such study was the Oxford Survey of Childhood Cancers, a case-control study of all children dying of cancer in the United Kingdom under age 16 years and matched controls. Exposure status was determined based on maternal recollection and was largely confirmed by prenatal records (24,25). The smaller sample size in this study was counterbalanced by the case-control design and increased radiation sensitivity of the population exposed before birth, and ERR for in utero exposure was 0.39 (0.30, 0.49). Several similar

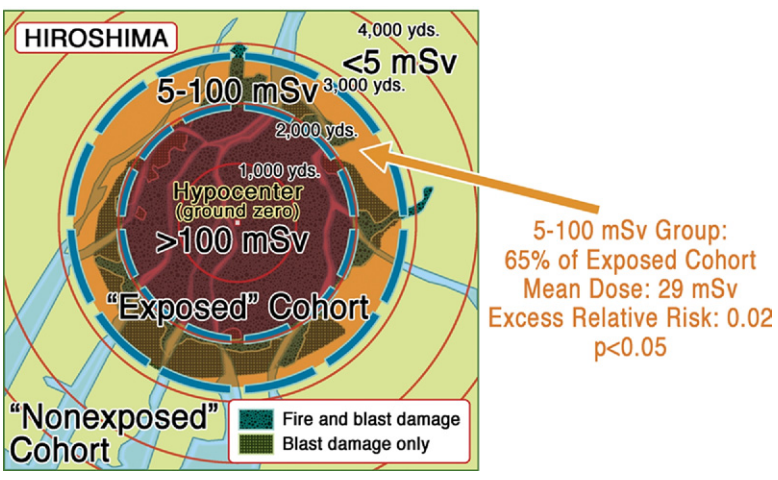

Figure 6 Simplified Hiroshima Atomic Bomb Dosimetry

Map of Hiroshima is overlaid with colors reflecting typical patient doses at distance from hypocenter. The **red circle** constitutes the area in which typical colon dose was at least 100 mGy (effective dose at least 100 mSv), and the **orange ring** constitutes the area with typical effective dose of 5 to 100 mSv; together, these roughly correspond to the "Exposed" cohort. The **green area** constitutes the area with typical effective dose of <5 mSv, roughly corresponding to the "Nonexposed" cohort. Significantly more cancers have been observed in the **orange ring** than would be expected based on rates in the **green area**, an excess that is attributed to ionizing radiation. The actual current dosimetry system, updated in 2002, reflects several factors in addition to distance from the hypocenter, including shielding history and information on acute effects such as burns and epilation. Hiroshima map without overlays have been reproduced with permission from the AtomicArchive.com website: http://www.atomicarchive.com/Maps/HiroshimaMap.shtml.

studies in various regions of the United States had very similar findings. This entire literature was reviewed by Richard Wakefield and Sir Richard Doll, arguably the leading epidemiologist of the 20th century, who demonstrated the connection between smoking and lung cancer and heart disease. They concluded that "a causal explanation is supported by evidence. . . radiation doses of the order of 10 mGy received by the fetus in utero produce a consequent increase in the risk of childhood cancer" (26).

SMALLER, HIGHER-DOSE STUDIES OF MEDICALLY EXPOSED COHORTS. Although the 3 very-low-dose studies mentioned in the previous text all found increased cancer risk at doses typical for some cardiac imaging patients, they did not involve exposure of adult patients to medical radiation. Although the putative mechanism of tumorigenesis in these studies is the same as that which could occur in cardiac patients receiving radiation, namely causality of DNA damage via an ionization event, subsequent genetic mutations, or chromosomal mutations from DNA damage misrepair, and ultimately the development of cancer (9), and thus this evidence is highly suggestive that cardiac procedures have the possibility of causing cancer, many practitioners would be more comfortable drawing such a conclusion from epidemiological data deriving from radiation exposure scenarios more akin to cardiac imaging and intervention. Indeed, there are a number of patient populations for which we have strong epidemiological data relating medical radiation to cancer risk; unfortunately the typical cumulative radiation doses received by individuals in these populations are considerably higher than those received by many of our cardiology patients, a necessary condition to enable adequate statistical power at smaller sample sizes.

Until the 1960s, radiation therapy was a relatively common treatment for numerous benign diseases, and considerable radioepidemiological data exists from these patients. Table 3 summarizes studies evaluating thyroid cancer risk after childhood radiotherapy for a variety of conditions (27–38). Although thyroid dose received by patients in these studies spanned 2 orders of magnitude, with mean doses as low as 100 mGy, excess risk per Gy received is generally compatible among these many studies, and with only a single exception, always statistically significantly >0. These studies evidenced a linear dose-response relationship and no lower threshold below which there was no increased risk, that is, consonance with the Linear No-Threshold (LNT) model (27). Similarly, numerous cohorts of patients undergoing medical radiation have been studied for excess breast cancers. These include patients in Massachusetts (39,40) and Canada (41) receiving repeated chest fluoroscopies as part of pneumothorax therapy for tuberculosis, patients in Gothenburg (38) and Stockholm (42) receiving gamma-rays for skin hemangioma, and patients receiving therapeutic x-rays for post-partum mastitis in New York (43), benign breast disease in Sweden (44), and thymic enlargement in Rochester, NY (45). Breast doses to subjects in these studies ranged from 20 mGy to 35 Gy, with mean doses ranging from 170 mGy to 5.8 Gy. Excess cancer risk was noted in each of these cohorts, and risk generally increased with attained age until about age 50 years at which point it plateaued in several studies (Fig. 7). The authors of a systematic review of most of these data (46) concluded that excess risk of breast cancer depends linearly on dose with a downturn at high doses, where cell death may occur, and that risk is similar between acute and fractionated high-dose-rate exposures, but lower with protracted low-dose rate exposures, although others have alternatively interpreted some of this data to conclude that fractionation also somewhat reduces risk (47). These studies were also generally compatible with the Life Span Study in terms of excess cancer rates (Fig. 7) (40,46), although there was some variation in rates between studies, leading the authors of the systematic review to point out that "no simple unified summary model adequately describes the excess risks in all groups" (46).

In addition to the studies evaluating thyroid and breast cancer, several other studies have evaluated risks of individual cancers from radiation to medically exposed cohorts. For the most part, these studies demonstrate excess cancer rates

Table 3 Epidemiological Studies of Thyroid Cancer After Childhood Radiotherapy

Study	Mean Dose (Gy)	ERR/Gy	EAR (10^4 Person-Year·Gy)$^{-1}$
Childhood cancer (28)	12.0	4.5 (3.1–6.4)	0.4 (0.2–0.5)
Tuberculosis, adenitis (29)	8.2	37.0 (16–72)	7.7 (3.3–15)
Chicago head and neck (30)	4.5	12.0 (6.6–20)	3.5 (2.0–5.9)
Thymus adenitis (31)	2.9	4.5 (2.7–7.0)	1.2 (0.7–1.8)
Rochester enlarged thymus (32)	1.4	9.5 (6.9–13)	3.0 (2.2–4.0)
Michael Reese enlarged tonsils (33)	0.6	3.0 (2.6–3.5)	38.0 (32–43)
Stockholm hemangioma (34)	0.3	4.9 (1.3–10)	0.9 (0.2–1.9)
Lymphoid hyperplasia (35)	0.2	5.9 (1.8–12)	9.1 (2.7–18)
Israel tinea capitis (36)	0.1	34.0 (23–47)	13.0 (9.0–18)
New York tinea capitis (37)	0.1	7.7 (<0–60)	1.3 (<0–10)
Gotenburg hemangioma (38)	0.1	7.5 (0.4–18)	1.6 (0.09–3.9)

Ranges in parentheses denote 95% confidence intervals. Reproduced with permission of Wolters Kluwer Health from Ron (27).
Abbreviations as in Table 2.

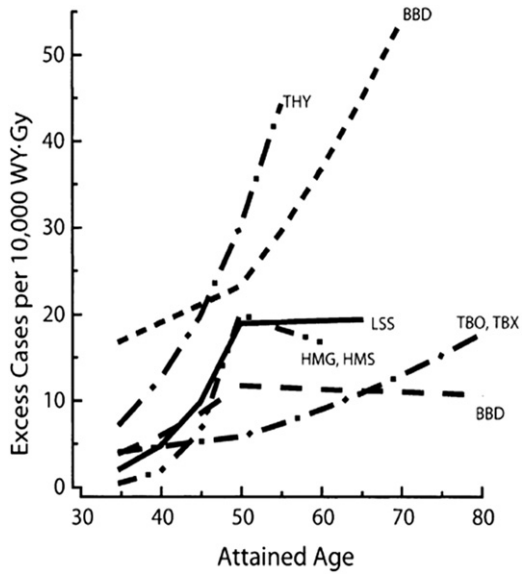

Figure 7 **Excess Breast Cancer Rate per WY·Gy Using Excess Absolute Risk Models**

Comparison of Life Span Study (LSS) of Japanese atomic bomb survivors to medically exposed cohorts. THY denotes thymic enlargement cohort (45); BBD benign breast disease (44); HMG, HMS hemangioma in Gothenberg (38) and Stockholm (42), Sweden, respectively; and TBO, TBX original (41) and extended (40) Massachusetts tuberculosis cohorts, respectively. Reproduced with permission of the Radiation Research Society–BioOne, from Preston et al. (46). WY = woman-years.

similar to those in the Life Span Study (Table 4) (48–53). However, in a few cases, no increased risk of individual cancers was demonstrated. In a study of 15,577 U.K. ankylosing spondylitis patients diagnosed between 1935 and 1957, patients receiving radiotherapy had a significant excess cancer mortality risk of 0.30 (0.24 to 0.35) above that expected from national rates, and significant increases individually for many, but not all organs (49). In both the Massachusetts (54) and Canadian (53) chest fluoroscopy cohorts, despite significantly increased rates of breast cancer that were consistent with Life Span Study data and increased linearly with dose (40,55), lung cancer risk was not increased. Various approaches have been offered to account for this discrepancy, including the amelioration of excess lung cancer risk by fractionation (9,53,54), and the modification of radiation-related risk in organs directly affected by disease, such as tuberculous lungs (9,53).

QUEBEC POST-MI STUDY. There is 1 recent study evaluating a cohort that received both very-low doses and radiation specifically from cardiac imaging and interventional procedures (56). This study used a Quebec hospital discharge summary database to create a retrospective cohort of 82,861 patients with acute myocardial infarction (MI) between April 1996 and March 2006 with no cancer diagnosis in the year before and year after this hospital admission. This data was linked to a health insurance database to identify billing codes for procedures performed involving ionizing radiation. No patient-specific dosimetry or organ dosimetry was estimated, but rather a typical effective dose was assigned for each of 4 specific cardiac procedures: myocardial perfusion imaging (15.6 mSv), diagnostic cardiac catheterization (7.0 mSv), percutaneous coronary intervention (15.0 mSv), and resting ventriculography (7.8 mSv). Cancers were identified beginning 1 year after MI based on International Classification of Diseases codes, and there was a mean follow-up of 5.0 years. The authors found that radiation exposure from cardiac procedures was 5.3 mSv/patient-year, of which 40% was from percutaneous coronary intervention, 30% from myocardial perfusion imaging, and 24% from diagnostic catheterization, with 84% of radiation in the first year post-MI. Mean exposure from noncardiac procedures was 1.6 mSv. There were 12,020 incident cancers in the cohort. In a time-dependent Cox proportional hazards model adjusting for age, sex, and exposure to low-dose ionizing radiation from noncardiac procedures, cumulative estimated dose from cardiac procedures was an independent predictor of incident cancer (hazard ratio: 1.003 per mSv, 95% confidence interval: 1.002 to 1.004). Thus, for every 10 mSv of radiation, the authors estimated a

Table 4 **Comparison of Estimated ERR/Gy Between Selected Medical Studies and the LSS of Japanese Atomic Bomb Survivors**

Cancer Site	Medical Study	Sex	Mean Organ Dose, Gy	Exposed Cases, N	ERR/Gy Based on Medical Study (95% CI)	Comparable ERR/Gy From LSS Cohort (95% CI)
Stomach	Cervical cancer (48)	Females	2	348	0.54 (0.05–1.5)	0.48 (0.31–0.73)
Stomach	Ankylosing spondylitis (49)	Males (83%)	2.5	127	−0.004 (<0–0.05)	0.21 (0.11–0.40)
Colon	Uterine bleeding (U.S.) (50)	Females	1.3	75	0.51 (<0–5.6)	0.43 (0.19–0.96)
Colon	Uterine bleeding (U.K.) (51)	Females	3.2	47	0.13 (0.01–0.26)	0.43 (0.19–0.96)
Lung	Peptic ulcer (52)	Males (80%)	1.8	125	0.24 (0.07–0.44)	0.32 (0.15–0.70)
Lung	Fluoroscopy (53)	Males	1.0	347	0.02 (<0–0.11)	0.32 (0.15–0.70)
Lung	Fluoroscopy (53)	Females	1.0	108	−0.06 (<0–0.07)	1.40 (0.94–2.1)
Prostate	Ankylosing spondylitis (49)	Males (83%)	1.5	88	0.14 (0.02–0.28)	0.12 (<0–0.69)
Bladder	Ankylosing spondylitis (49)	Males (83%)	1.5	71	0.24 (0.09–0.41)	0.50 (0.18–1.4)

Data are for organs other than breast and thyroid. To be included here, sites had to meet the following criteria: 1) the BEIR VII committee provided cancer risk estimates; 2) the study investigators presented estimates of the excess relative risk (ERR)/Gy; 3) the mean dose to the organ of interest was <4 Gy; and 4) the estimate was based on at least 30 exposed cases. For the Life Span Study (LSS), estimates are sex-specific estimates from BEIR (Biological Effects of Ionizing Radiation) VII Table 12-3 (for the sex indicated in column 3) and are for exposure at age 30 years at attained age 60. Reproduced with permission from the National Academies Press, BEIR VII Table 12-11 (9). Copyright 2006, National Academy of Sciences.

3% increase in risk of age- and sex-adjusted cancer over the mean 5-year follow-up, suggesting that in post-MI patients "exposure to low-dose ionizing radiation directly affects the likelihood of cancer."

Although the conclusions of this study are provocative, several highly unusual findings and methodological concerns have been pointed out, and many experts believe that until further analyses are presented, the study findings must be regarded as preliminary (57). The effect noted in the study is an order of magnitude greater than in other epidemiological studies of adult radiation exposure. Cancer incidence in the cohort was at least 2 times the expected incidence in the Canadian public. Solid tumors (92% of the cancers in the cohort) typically occur only after a 5- to 10-year latency period after radiation exposure (9), yet mean follow-up here was only 5 years. Confounders such as smoking were not accounted for. Analysis was performed using an estimated effective dose, and there was no study of the relationship between organ dose and organ-specific cancer. Estimated effective doses were those for a typical dose from a procedure and did not reflect radiation received by the individual patient, for example, the 15.6 mSv estimate for all myocardial perfusion imaging exams is a figure reflecting a U.S. prevalence–weighted average of typical effective doses from standard protocols ranging from stress-only tetrofosmin (7.2 mSv) to thallium rest-reinjection (30.1 mSv) (58). Thus, in the absence of further analyses, including demonstration of association between site-specific cancers and organ-specific doses, explanation of the high baseline cancer incidence, and presentation of cancers by latency period, the possibility remains that the study's findings represent a spurious association unrelated to cancer causality.

ONGOING STUDIES. In addition to the completed studies presented in the previous text, there are a number of ongoing large epidemiological studies of very-low-dose medical radiation that will further refine our understanding of radiation-associated cancer risk. These mostly focus on children who underwent computed tomography. The increased sensitivity of children to radiation-induced cancer enables such studies to be performed with much smaller sample sizes than in adults. The first of these studies, expected to report initial results in the next year, is evaluating a cohort currently of about 250,000 individuals under age 22 years in the United Kingdom, and includes individual-level outcome data, dosimetric modeling reflecting patient information collected from radiology departments and scanner- and protocol-specific information (59,60). Additional similar studies are being conducted, including in Ontario, Canada (~275,000 children), Australia (150,000), Israel, and several European countries, and the World Heath Organization's International Agency for Research on Cancer is coordinating a European collaborative study, incorporating over a million children, called EPI-CT (Epidemiological Study to Quantify Risks for Paediatric Computerized Tomography and to Optimise Doses). Another study in the United Kingdom, just beginning, will evaluate cancers in a cohort of children who underwent interventional cardiology procedures.

Applying epidemiological data to estimating cancer risk from cardiac imaging. Given the absence of direct evidence from cardiac imaging, current risk estimates for cardiac imaging procedures are in fact projections from the available epidemiological evidence. This evidence base has been comprehensively reviewed several times since the 1950s by a series of expert committees on the Biological Effects of Ionizing (formerly Atomic) Radiation, now known by the acronym BEIR, that have been convened by the U.S. National Academies. Their most recent report, BEIR VII, was released in 2005, and reflected all of the aforementioned literature that was then available (the 15-Country Study became available only after the draft report had been reviewed, and the Quebec Post-MI study had not been conducted) (9). The BEIR VII committee's comprehensive review led them to conclude, with caveats and like the other major U.S. and international advisory organizations, that the LNT model best fits the currently available data for purposes of radiation protection (61). Thus, despite widespread misunderstanding to the contrary, LNT is not regarded as reflecting a conservative approach to estimating risk from low-dose radiation exposure (i.e., an upper estimate of risk), but rather the best simple model given the currently available data.

In particular, BEIR VII devoted an appendix to addressing the evidence relating to the concept of "hormesis," which posits that low doses of radiation provide a beneficial health effect by means of adaptive protection, stimulating DNA damage prevention and repair as well as immune stimulation (62). This analysis concluded that it is unwarranted to assume that any such hormetic effects from low-dose radiation have significant health benefits to humans that outweigh radiation's detrimental effects (9).

BEIR VII developed LNT-assuming risk models for cancer incidence and mortality, applicable to the general U.S. population, that can be used in conjunction with estimates of organ doses to estimate cancer risk from specific medical exposures. These models are largely based on data from the Life Span Study, although the pooled breast cancer model from the systematic review discussed in the previous text (46), and a thyroid cancer model (63) based on several of the medical studies tabulated in the previous text (63), are incorporated. BEIR VII risk projection models have been applied to several cardiac imaging scenarios to estimate cancer risk to patients and populations. My colleagues and I applied BEIR VII models to estimation of cancer risk from coronary CT angiography using a helical protocol, finding radiation-attributable risks that varied widely depending on patient age, gender, and scan protocol (Fig. 8), which were roughly 1 in 3,000 in older men but approached 1% in young women (64). This analysis was subsequently repeated by Huang et al. (65) after the introduction of prospectively triggered CT angiography, demonstrating patterns of risk

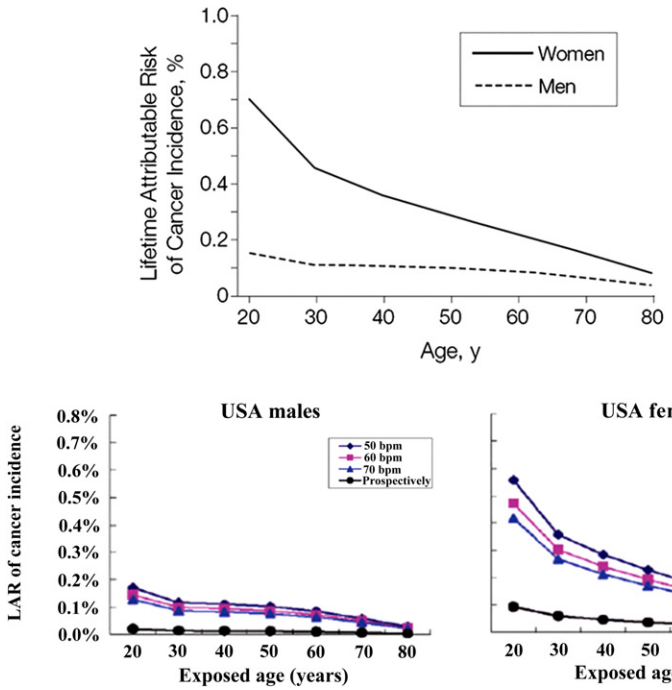

Figure 8 Estimated Risk of Cancer Incidence Attributable to Coronary CT Angiogram

(Top) Estimates from Einstein et al. (64). Copyright 2007 American Medical Association. All rights reserved. **(Bottom)** Estimates from Huang et al. (65) (reproduced with permission of the British Institute of Radiology), which are comparable to those of Einstein et al. (64) and demonstrate markedly lower risk with prospectively triggered protocol. All estimates are for retrospectively gated helical scanning except for estimates labeled "prospectively" in the **bottom panel**. bpm = beats per minute; LAR = lifetime attributable risk.

for prospectively triggered scanning that mirrored those for helical scanning, but with absolute risks reduced roughly proportionally to the ~80% reduction in dose. Kim et al. (66) have applied BEIR VII methodology to screening with coronary artery calcium scoring, finding that every-5-year screening as advocated by the Screening for Heart Attack Prevention and Education (SHAPE) guidelines would be associated with an estimated 42 cancers per 100,000 men screened and 62 per 100,000 women, estimates that can be compared with potential benefits from screening. Berrington de Gonzalez et al. (67) have applied BEIR methodology to estimating cancer risks from myocardial perfusion imaging, demonstrating, analogously to Huang et al., that reduced-dose nuclear stress testing protocols are associated with reduced estimated cancer risks.

Thus, BEIR VII risk projection models offer a practical tool to estimate radiation risk from cardiac imaging procedures, to be considered in the context of an analysis of benefits, risks, and costs. Nevertheless, even beyond the LNT assumption, several assumptions underlie these models that render their risk projections approximate values with associated uncertainty. These models transport data from a healthy Japanese to a healthy U.S. population, and assumptions need to be made as to how to account for differences in baseline cancer rates. Application of BEIR models to populations with decreased life expectancy in comparison to the general U.S. population, as is the case for many populations of patients undergoing cardiac imaging and intervention, will result in overestimates of radiation-attributable cancer risk, and consequently estimates of the total number of cancers attributable to such procedures may also be overestimates. Although methods have been introduced to adjust risks based on clinically determined life tables (Fig. 9) (68), such life tables are not available for many populations of interest. X-rays used in medical imaging may have differences in tumorigenic potential in comparison to the high-energy gamma-rays from atomic bombs (69), and risk models need to incorporate a choice as to how to approach this potential difference. There is an assumed factor used to extrapolate data from acute high-dose to low-dose exposures, the selection of which is a matter of some debate. Assumptions are made as to the forms and sizes of dose uncertainties (9).

Each assumption made was based on exhaustive consideration of all available biophysical as well as epidemiological evidence by a team of experts who are world-class scholars of radiation biology, physics, and epidemiology, and who were accountable to multiple feedback mechanisms. Although it has become popular in some cardiovascular circles to minimize the potential problem of ionizing radiation exposure by emphasizing the uncertainty inherent in these assumptions, foremost among them the LNT model, I

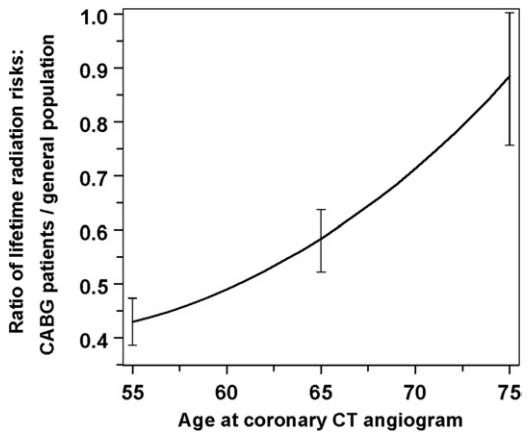

Figure 9 **Reduction of Cancer Risk From Coronary CT Angiography in Post-CABG Patients in Comparison to Healthy Patients**

Shown are data from post-coronary artery bypass graft (CABG) patients in comparison to healthy patients. Error bars show 95% confidence intervals on the estimated risk ratio. Reproduced with permission of the Radiological Society of North America from Brenner et al. (68). CT = computed tomography.

would respectfully suggest that the collective expertise found in the National Academies' BEIR VII committee pertinent to addressing these issues exceeds that in our cardiology community. Although BEIR VII models most admittedly estimate phantom cancers in phantom patients, and rest on evidence-based assumptions that may at some future date be demonstrated to be erroneous, they provide the best framework available today for estimating the radiation risks that may offset in part the multitudinous benefits of cardiac imaging and intervention.

Effects of radiation exposure from cardiac imaging: how good are the data? In summary, no strong data currently relate ionizing radiation specifically from cardiac imaging to increased risks of cancer. Nevertheless, several landmark epidemiological studies involving similar levels of radiation exposure all show increased cancer risk, and allow risk projection. All low-dose and most high-dose studies show increasing cancer risk with increasing radiation dose, although there are a few exceptions, notably studies of lung cancer in cohorts who underwent repeated fluoroscopy as part of pneumothorax therapy for tuberculosis. BEIR VII risk projection models, although based on multiple assumptions, best fit the available data and can be used to estimate cancer risks associated with cardiac imaging. Nontrivial risks that have been described in some scenarios underscore the importance of justification of all studies involving ionizing radiation, a goal towards which appropriate use criteria (70,71) and guidelines (72) can serve as valuable tools. The reduction in estimated risk that has been shown to parallel reduction in dose underscores the importance of dose optimization using the ALARA (As Low As Reasonably Achievable) principle (6), which to implement necessitates continual improvement in protocols, equipment, and training to ensure best practice. Several important ongoing epidemiological studies involving over a million individuals exposed to medical radiation will provide us with a fuller picture as to the true effects of radiation exposure from cardiac imaging.

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Key Words: cardiac imaging ■ epidemiology ■ radiation exposure.