RADIATION EXPOSURE AND REDUCTION (R SEMELKA, SECTION EDITOR)

# CT Radiation and the Risk of Cancer

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Abstract The paper covers three points. First, the doses we use for CT are higher than widely reported and are higher than what is needed for diagnosis and should be reduced. Second, these doses are in the range where extensive evidence indicates they will cause enough cancers to support efforts to reduce dose and therefore this risk. Third, that precise quantification of the risks from imaging radiation is less important than understanding that the risks are real, albeit small, and worth reducing, and that this reduction must be achieved using systems-based approaches.

Keywords CT radiation · Cancer · Risk · Systems-based approaches

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#### Introduction

As health care providers, we know that medicine involves tradeoffs. When deciding about a diagnostic exam, new medication, or surgical procedure, we must balance potential benefits to patients with potential harms. Until recently, with the exception surrounding a few invasive procedures, radiologists have not been closely involved in risk–benefit discussions. In general, radiologists and our referring colleagues have been so enthusiastic about the rapid improvements in imaging technology that we have assumed the benefits out weigh the harms. While early and accurate diagnosis is beneficial, the potential harms of imaging are also significant: overdiagnosis leads to overtreatment  $[1, 2]$  $[1, 2]$  $[1, 2]$  $[1, 2]$ , false positives  $[3]$  $[3]$  trigger a cascade of testing, and radiation exposure increases cancer risk [\[4](#page-5-0)]. Fortunately, patients are starting to demand more information about their care [\[5](#page-5-0)] including information about medical diagnostic procedures. Radiologists are beginning to discuss the need to educate our patients and ensure they understand testing tradeoffs [\[6](#page-5-0), [7](#page-6-0)]. And payers now want to know about specific imaging benefits and harms when considering covering medical imaging, illustrated by the ongoing discussion about whether the Center for Medicare and Medicaid Services will pay for lung cancer screening with low-dose CT [8-10]. A handful of radiologists and medical physicists are indignant over risk–benefit discussions about medical imaging fearing that this will lead to patients declining what they perceive as ''needed imaging.'' However, current research indicates that patients want detailed information about their care and shared decision making is becoming not only common, but an expectation of quality clinical practice [\[5](#page-5-0)]. Further, several studies have found patients make appropriate and informed choices when provided with good information about

medical imaging [[11\]](#page-6-0). We cannot maintain the paternalistic doctor–patient relationship of past decades and simply make medical decisions for patients or, perhaps even worse, minimize description of risks. Even if our intention seems laudable we cannot prevent people from refusing recommended tests if that is their choice. The modern approach requires that we ensure that patients are involved in decisions about medical imaging, and have a reasonable understanding about risks. Sharing risk–benefit information is particularly important for computed tomography, given how frequently it is used  $[12]$  $[12]$ , and overused  $[13, 14]$  $[13, 14]$  $[13, 14]$  $[13, 14]$  $[13, 14]$ . In this paper, epidemiological data on radiation risk will be reviewed, and three points will be covered: first, the doses we use for CT are higher than widely reported and are higher than needed; second, that these doses are in the range where extensive evidence indicates they will cause enough cancers to support efforts to reduce the doses and therefore this risk; and third that precise quantification of the risks from imaging radiation is less important than understanding that the risks are real, albeit small, and worth reducing, and that this reduction must be achieved using systems-based approaches.

## The Epidemiological Approach

No cancer-causing agent has been studied more than ionizing radiation, including doses in the range that we frequently use for medical imaging with CT. Much of what we know about the harmful effects of radiation comes from epidemiological studies [\[15](#page-6-0)••, [16](#page-6-0)••, [17](#page-6-0)••, [18](#page-6-0)]. Epidemiology is a science of disease patterns, causes, and risk factors and is the cornerstone of public health. Epidemiology informs health policy as well as individual physician– patient interactions. It aims to guide evidence-based medical decisions by identifying risk factors for disease and targets for prevention and quantifying medical risks and benefits.

Epidemiology assesses the impact of risk factors in populations; it does not explain every case of illness. Two illustrative examples highlight the epidemiological approach. First, in 2012, a multi-state outbreak of fungal meningitis and other infections occurred in associated with injection of contaminated methylprednisolone that was purchased from a single compounding pharmacy [\[19](#page-6-0)]. More than 13,500 people had injections with the contaminated drug and over 700—about 6 %—got sick, including deaths in 61. Based on the initial identification of 8 affected patients, an intense national investigation was begun, the contaminated drug was identified and recalled, and the pharmacy responsible for the contamination was closed.

As a second example, consider the association between smoking and lung cancer. In the US, approximately 20 % of the U.S. population smokes, and thus for a hypothetical population of 1,000 US individuals, imagine one group is comprised of 200 smokers and one group is comprised of 800 non-smokers. By age 75, approximately 30 of the 200 smokers and 8 of the 800 non-smoker will develop lung cancer (Fig. 1) [\[20](#page-6-0)]. There are many ways to quantify the elevated risk of lung cancer in smokers including absolute risk; the absolute risk of lung cancer is 15 % in smokers and 1 % in non-smokers. Relative risk compares risk in one group with another group—the relative risk of developing lung cancer is 15, defined as 15 % risk in smokers divided by the 1 % risk in non-smokers. This might be summarized as saying smokers are 15 times more likely to develop lung cancer than non-smokers. Excess relative risk, is defined as how much additional risk is associated with an exposure, in this case excess relative risk is 14 % (15 % risk in smokers minus 1 % risk in non-smokers). Similar measures are used below to quantify the risk of CT scans. Of note, for both lung cancer and meningitis, most patients are not affected, and it is at present impossible to identify the person likely to become diseased. This is essentially the same circumstance with ionizing radiation and medical imaging. No one would trivialize the risks related to the contaminated injections by saying that ''fewer than 1 percent of patients were affected'' as is often done when discussing the potential risk of radiation. In epidemiology, a 1 % risk is important because few single factors have such a quantifiable major population impact. While radiation exposure may not have an impact on cancer risk for many years after exposure (which is similar to smoking as the cancer induction also takes a period of years after the initiation of smoking), its potential for causing harm is no less important despite the delay.



Fig. 1 Risk of lung cancer mortality among men in the United Kingdom by smoking status, based on data from Vineis et al. [\[20\]](#page-6-0)

## Typical CT Exposures

Understanding the potential risks of CT radiation requires knowing the approximate exposures. Numerous reports have documented that doses for CT tend to be higher and more variable than widely reported, and can vary 50-fold or more for patients imaged for the same clinical indication across institutions [\[12](#page-6-0), [21–24](#page-6-0), [25](#page-6-0)•]. For example, abdominal CT scan is typically cited as using 8 mSv [\[26](#page-6-0)], but we have reported that average abdominal CT doses at an institution can be as high as 45 mSv depending on indication [[21\]](#page-6-0). Among children, high doses can be even more harmful than in adults [[13](#page-6-0)] and are also highly variable. For example, among children enrolled in an HMO, the doses for abdominal CT scanning in children aged 1–4 years ranged between 4.8 and 137 mSv for a single study [\[24](#page-6-0)]. Further, the type of institution can influence the doses patients receive. For example Sharp reported to the American Academy of Pediatrics that children receiving CT scans at non-pediatric hospitals received radiation doses that were, on average, 8 times the doses from CT at pediatric facilities, and thus where CTs are obtained is strongly associated with the doses that will be received. Only a small part of the variation in doses is due to the appropriate accommodation of patients of difference sizes [\[24](#page-6-0)], and most of the variation reflects physician and technologist preferences. For example, there is dramatic variation in how often multiphase scanning is used (something that profoundly influences dose), and yet little scientific evidence of improved diagnoses associated with their use.

In the collaborative University of California Dose Optimization and Standardization Endeavor project (UC-DOSE project), funded by the University of California Office of the President, we are prospectively pooling CT radiation dose data from the five University of California medical centers to study CT radiation doses across protocols and anatomic area [[27\]](#page-6-0). So far, we have assembled data on more than 400,000 CT scans since 2012. Our preliminary results again indicate a broad range of patient radiation doses from CT, and, as with other reports, have found the doses much higher and more variable than widely cited. For example, we found the doses for abdominal CT scans use an average effective dose of 17 mSv, where 25 % of adult patients received a dose for a single abdominal CT scan above 26 mSv. The doses that patients receive will vary by the protocols that are chosen, and the protocols themselves have widely varying doses. As part of this project, we identified the most frequently used protocol within each anatomic area, at each of the five sites. Using the example of an abdomen study, while at one institution the most commonly used abdominal imaging protocol in adults was associated with a median effective

dose of 5 mSv (range 2–43 mSv), at another institution the most commonly used abdominal protocol was associated with a median effective dose fourfold higher [21 mSv (range 4–49)]. The highest abdominal protocol was associated with a median dose of 43 mSv (range in the dose of this protocol 14–100 mSv effective dose). We are currently working to understand the variation in dose, and while patient size is an important predictor of dose (larger patients receive higher doses), patient size does not explain the variation in dose across sites, and the largest contributor to the highest doses that patients received was not patient size. For abdominal and chest studies in the U.S., patients are frequently exposed to doses in the 20–50 mSv range, and frequently receive abdominal and chest organ doses in the 20–50 mGy range.

# Harms of Current CT Radiation Doses

Extensive epidemiological and biological evidence demonstrates that exposure to radiation in the same range as that delivered by CT [10–100 milli-Sieverts (mSv)] increases a person's risk of developing cancer [[15](#page-6-0)••, [16](#page-6-0)••, [28–30\]](#page-6-0). The evidence comes from diverse studies, including studies of the Hiroshima and Nagasaki survivors (A-bomb) survivors; patients radiated in utero while their mothers underwent diagnostic testing; secondary cancers in patients treated for benign or malignant disease; repeated diagnostic X-ray exposures; occupational exposures; individuals who have been exposed to environmental settings; and recently two cohort studies demonstrated a tripling in the risks of leukemia, brain cancer, and solid cancers associated with exposure to CT in children and young adults [\[17](#page-6-0)••, [31](#page-6-0)]. Several of these studies and several reviews of the studies are highlighted in greater detail below.

The 2006 BEIR VII (Biological Effect of Ionizing Radiation VII) Report from the National Academy of Sciences Committee assessed the health risks ionizing radiation at doses below 100 mSv [[15](#page-6-0)••]. This comprehensive review summarized the primary data sources on radiation risks that would be important to consider, and summarized the results of hundreds of studies. The committee concluded that radiation doses in the 10–50 mSv range—the same range as frequently used with CT—causes cancer in some individuals. Further, the report provides quantitative estimates of the risks, as well as uncertainties of the risk estimates, using a broad range of assumptions. A recent literature review from the United Kingdom (UK) Health Protection Agency [[32](#page-6-0)••] provides easily understandable tables of the results of the various studies, and supports the same conclusion. Using the cancer risk estimates from the BEIR VII report, numerous researchers have estimated the risk of cancer from CT, using data from

<span id="page-3-0"></span>observed CT dose data. These have found that the risk of cancer from observed levels of radiation used for CT can be as high as an absolute risk of 1 % for abdominal CT due to the high doses that are used  $[21, 24]$  $[21, 24]$  $[21, 24]$  $[21, 24]$  $[21, 24]$ , although this will vary by age at exposure and dose. It has been estimated that overall 2–5 % of future cancer may be attributable to exposure to medical imaging and that 30,000 future cancers can be expected to result from 1 year of current CT exposures [[33,](#page-6-0) [34](#page-6-0)].

Preston reported additional follow-up on the Life Span Cohort Study of A-bomb survivors after the publication of the BEIR VII report. This report includes longer follow-up of the 105,427 surviving individuals, including over 17,448 first cancers that were diagnosed between 1958 and 1998. Radiation-associated relative risks were calculated for all solid cancers as a group, and for individual cancer types. Because of the longer follow-up, the analysis allowed improved estimates of the cancer risks—as cancers continue to accumulate with longer time since exposures—and was able to quantify the risk of cancer in different groups by age at exposure, sex, and time of follow-up. The median radiation exposure received by these survivors was 40 mSv, similar in magnitude to many patients who undergo CT. Most of the exposures in the cohort were in the 5–200 mSv range and only 1 % of the cohort had exposures above 1 Sv. Thus while it is commonly assumed that most A-bomb survivors had doses far higher than those we encounter with CT scanning, this is not true. Among the Life Span Cohort members with colon exposures above 5 mGy (colon being used as reflection of abdominal exposures; in the UCDOSE collaboration, colon doses from abdominal CT averaged 20–30 mGy), 11 % of solid cancers and 44 % of leukemias at the 25-year follow-up period were attributed to the radiation exposure. Furthermore, the authors found a statistically significant dose response when the analyses were limited to cohort members with doses of 150 mGy or less. The most recently updated Life Span Study results published in 2012 added another 5–7 years of follow-up and again confirmed that there was a significantly elevated absolute and excess relative risk of nearly every cancer type even among those with radiation exposures in the lowest dose exposure category of  $\leq$ 1–20 mSv[\[18](#page-6-0), [35](#page-6-0)].

The first direct study of the risk of cancer associated with CT was published in 2012. Pearce et al. [\[17](#page-6-0)••] performed a retrospective cohort study of 178,604 children and young adults in the UK who underwent CT scans between 1985 and 2002. These patients were followed through 2008 and 74 cases of leukemia and 135 cases of brain cancer were diagnosed in these patients. The authors assessed the relationship between estimated organ doses to the brain and bone marrow and excess brain cancer and leukemia. The authors controlled for factors that relate to both CT and cancer, and excluded cancers suspected to have been present prior to CT. Within 10 years of their first CT scan, children who received bone marrow or brain doses of 50–60 mGy tripled their risk of leukemia and brain cancer, respectively, in comparison with children who underwent a single CT. These are doses frequently encountered in children who undergo CT, particularly because many children undergo multiple scans. We found that over 10 % of children are exposed to bone marrow or brain doses of 30–50 mGy in a single exam [[24\]](#page-6-0). Figure 2 shows the risk of leukemia related to bone marrow doses in the Pearce study, and shows the range of doses for children who underwent two abdominal CT scans using dose estimates from the UCDOSE collaboration. We decided to use 2 abdominal CT scans as the basis for comparison, because in the US the average number of abdominal CT scans for patients who undergo any CT imaging is two [\[12](#page-6-0)]. The figure highlights that the elevated relative risk of cancer is in the range of doses we routinely use for CT. Of note, no extrapolation of data from high-dose exposures is performed or necessary, as the doses that patients receive when they undergo CT is in the range of directly observed evidence. Comparable data are shown for brain doses and excess brain cancer risk in Fig. [3.](#page-4-0) While the Pearce study has limitations, that included the fact that the study only included patients exposed to CT and did not have a comparison group without CT imaging, dose estimations were approximate and based on sample data, and they did not have adequate information on the reason for imaging; the study was a well-done observational trial, and none of these weaknesses reflects a major flaw. This important study demonstrates direct and valid evidence that CT scanning is associated with an increased risk of cancer.

Finally, a study of environmental exposure of Ukrainian clean-up workers who cleaned up after the 1986 Chernobyl nuclear plant accident examined cancers through 2006, documenting 137 leukemias among the exposed workers



Fig. 2 Relative risk of leukemia at around 10 years after CT, based on data from Pearce et al. [\[17](#page-6-0)••]

<span id="page-4-0"></span>

Fig. 3 Relative risk of brain cancer at around 10 years after CT, based on data from Pearce et al. [\[17](#page-6-0)••]

[\[36](#page-6-0)]. Estimates for the population showed average bone marrow doses of 132 mGy for cancer cases and 82 mGy for controls, with a substantial excess relative risk for leukemia for exposure doses similar to the radiation doses patients receive from CT. The authors conclude, ''Exposure to low doses and to low dose-rates of radiation from post-Chernobyl clean-up work was associated with a significant increase in the risk of leukemia, which was statistically consistent with estimates for the Japanese atomic bomb survivors'' [\[36](#page-6-0)].

#### Summary of Research on Radiation and Cancer Risk

The research on radiation varies in study design, source of exposure (medical or occupational), methods for dose measurement, and statistical techniques used to describe the relationship between exposure and cancers. The data are complex because of design issues and because cancer risks vary by sex, age of exposure, time after exposure, type of exposure, type of energy source, and individual risk factors that strongly affect cancer susceptibility. The limitations of the A-bomb survival data that complicate direct comparisons to CT have been described at length and include issues such as full versus partial body exposure, different kinds and levels of energy, and different underlying population cancer risks. This makes it impossible to precisely estimate the risk of CT imaging, when using data from other sources, and thus there is uncertainty in all estimates. Nonetheless, the various sources of estimates do provide remarkably statistically consistent and therefore highly believable results. For example, Pearce when directly assessing the risk of CT found the excess risk rate for leukemia was 0.036 per mGy and 0.72 per CT, whereas Preston estimated the excess risk rate for leukemia as 0.045 per mGy and 0.90 per CT; the numbers are remarkably similar, given the different methods and populations [[16](#page-6-0)••]. The overwhelming body of literature suggests that radiation doses of 10–150 mSv—including the 10–60 mSv range currently delivered frequently during CT—is carcinogenic, with higher exposure leading to higher risks for every type of cancer that has been studied.

One of the arguments that is used to discount the relevance of the A-bomb survival data to medical imaging relates to the linear no threshold (LNT) model. The LNT model was primarily developed for radiation protection purposes to explain the potential risks of low doses of radiation in dose ranges where there are few empirical data. This is particularly important for questions that relate to extremely low exposures such as those provided by a chest X-ray or backscatter airport scans where epidemiological data cannot provide quantified risk because the exposures are so small. However, the use of this model is not critical when discussing the risks of CT, as there are directly observed data where radiation associated with CT is carcinogenic, as shown in Figs. [2](#page-3-0) and 3.

Most of the risks of radiation exposure related to imaging are considered stochastic risk—i.e., involve uncertainty regarding who will develop the cancer. This is similar to the probabilistic risk of lung cancer among smokers, or risk of fungal meningitis among individuals who received tainted injections. The other risks of injury that arise relating to radiation dose occur at doses that are higher than those routinely used for imaging. At these higher doses, the harmful effect of the radiation—typically resulting in burns and tissue damage—will occur with greater certainty and at a more predictable threshold. These risks are typically called deterministic risks in radiology. It is important to note that in some cases, when imaging is done incorrectly, the doses of radiation can cause deterministic effects. For example, while the brain doses of radiation used for medical imaging tend to be in the 60 mGy brain dose range, patients who were over-radiated at Cedars-Sinai hospital in LA (where patients lost hair in a band-like distribution, and suffered acute radiation poisoning from the CT)—received doses over 6 Gy—100 fold higher- and in the same range as radiation used to treat cancer [\[37](#page-6-0)]. Deterministic effects are also observed in the setting of fluoroscopy-guided interventional or cardiology procedures, where extended use of fluoroscopy has occurred [\[38](#page-6-0)]. Overall, since the types of doses that are required for deterministic effects are rare, more individuals are at risk for stochastic effects.

# The Impact of Optimizing and Lowering the Doses Used for CT

The literature provides a preponderance of evidence that exposure to radiation in the range that is routinely used for <span id="page-5-0"></span>CT is carcinogenic. The literature also provides extensive evidence that doses are higher than needed for diagnosis. To illustrate this point, I included images from two CT scans for a patient who was evaluated as part of the National Lung Cancer Screening Trial in a recent publication [\[37](#page-6-0)]. The two chest CT scans were taken a year apart at the same institution for the same patient for the same purpose, surveillance of a pulmonary nodule. The images show no difference in diagnostic quality for the purpose of the nodule surveillance, despite using doses that vary by tenfold (1.5 vs. 15.9 mSv)

The American College of Radiology Dose Index Registry (DIR) recently reported on the doses that were used for kidney stone protocol CT that further highlights the inappropriate setting of dose on a larger scale  $[25\bullet]$  $[25\bullet]$ . Computed Tomography scans obtained for suspected kidney stones should use low-dose techniques, delivering doses around 3–4 mSv, as diagnostic accuracy is as good or better than when higher doses are used. Among nearly 50,000 renal colic protocol CT examinations included in the registry, only  $2\%$  of studies were conducted using appropriate low-dose techniques. These two examples one reflecting a single patient at a single institution and the second reflecting nearly 50,000 patients across over 90 institutions—highlight what most radiologists know to be the case: we are currently using CT doses that are higher than needed for diagnosis and are exposing patients to unnecessary risk. This points out the need for greater awareness that doses can be, and should be, reduced with little or no loss in image quality, thereby improving patient safety without any loss in the benefit of CT.

Miglioretti et al. conducted a retrospective cohort study using CT imaging records from Group Health Cooperative, an integrated health plan and care system in Washington State. She characterized patterns of imaging and radiation doses among the 5 million person years of data [[24\]](#page-6-0). Using these data they estimated that national CT use in children in 2010 will result in approximately 10,000 future cancers in these children. She also estimated the impact on the total number of cancers that would occur if the highest quartile of doses were reduced to the average—i.e., reduce the highest outlier doses and bring them to the mean. The estimate was that 44 % of those cancers would no longer occur. This is a very large potential benefit that would occur by standardizing and optimizing the doses used for CT.

I believe we have two choices as radiologists. We can deny that we have sufficient data to be concerned about risk of radiation and highlight the uncertainties involved in the estimates of risk and continue to focus solely on the beneficial side of the equation related to imaging. Under this approach, we can trust that every physicist and radiologist has the capacity to independently follow the principle of ALARA and individually determine the lowest reasonable CT dose for their patients, and that optimized doses will result. Alternatively, we can set concrete standards and create systems to ensure that radiologists, medical physicists, and technologists meet these standards. This approach recognizes that individual institutions and radiologists cannot be expected to comply with ALARA without systems to support their action. There are many steps that individual radiologists can take to standardize doses—and we have created a free online, virtual symposium on Radiation Safety and CT that provides concrete examples of how to standardize protocols [[27,](#page-6-0) [39](#page-6-0), [40](#page-6-0)•]. However, if we adopt a systems-based approach as a specialty, this will lead to a faster improvement in the safety of CT.

The time of denying that medical radiation has the potential to cause cancer, has long past. We are now in the age that we have to take ownership of this issue and make changes in how we conduct our practice. Some of these steps should be simple to implement, yet powerful, such as a continuously updating systems-based standardization to ALARA principles.

## Compliance with Ethics Guidelines

Conflict of Interest Dr. Rebecca Smith-Bindman declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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