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ARE RISKS FROM MEDICAL IMAGING STILL TOO SMALL TO BE OBSERVED OR NONEXISTENT?

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□ Several radiation-related professional societies have concluded that carcinogenic risks associated with doses below 50-100 mSv are either too small to be detected, or are nonexistent. This is especially important in the context of doses from medical imaging. Radiation exposure to the public from medical imaging procedures is rising around the world, primarily due to increased utilization of computed tomography. Professional societies and advisory bodies consistently recommend against multiplying small doses by large populations to predict excess radiation-induced cancers, in large part because of the potential for sensational claims of health impacts which do not adequately take the associated uncertainties into account. Nonetheless, numerous articles have predicted thousands of future cancers as a result of CT scanning, and this has generated considerable concern among patients and parents. In addition, some authors claim that we now have direct epidemiological evidence of carcinogenic risks from medical imaging. This paper critically examines such claims, and concludes that the evidence cited does not provide direct evidence of low-dose carcinogenicity. These claims themselves have adverse public health impacts by frightening the public away from medically justified exams. It is time for the medical and scientific communities to be more assertive in responding to sensational claims of health risks.

Key words: medical imaging; linear no-threshold hypothesis; radiation risk; atomic bomb survivors; computed tomography

INTRODUCTION

It has recently been claimed that we now have direct evidence of carcinogenic risks associated with medical imaging (Brenner and Hall 2012), and rarely a week goes by without the publication of a study [*e.g.* (Berrington de Gonzalez *et al.* 2009; Smith-Bindman *et al.* 2009; Miglioretti *et al.* 2013)] or newspaper article (Redberg and Smith-Bindman 2014) warning of thousands of future cancer cases caused by medical imaging. How much credence should patients, parents, and healthcare practitioners put in these claims?

Referring physicians are called upon to ensure that there is a clinical need for the information to be provided by any imaging exam involving exposure to ionizing radiation, (Brody *et al.* 2007; IAEA 2009; Rehani 2012; Esz 2013). In the international radiation protection framework,

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this process is formally known as "justification". In order to make a sound justification decision, an accurate understanding of both the benefits and risks of the exam are required. There is little disagreement that medical imaging exams should be appropriately justified, and it is widely recognized that the benefits almost always outweigh any risks of imaging exams for medically indicated exams, except in the case of redundant exams (Valentin 2001; IAEA 2009). For example, repeat exams because of poor record-keeping or lack of ready access to patient records are difficult to justify. Similarly, imaging exams for the purpose of defensive medicine are not in the interest of the patient, and do not satisfy the justification requirement. The determination of when medical imaging exams involving ionizing radiation are justified, by balancing observed benefits versus projected risks [*e.g.* (Berrington de Gonzalez *et al.* 2008)], is directly dependent on how risks are estimated. If risks are overestimated, then access to medical imaging may be inappropriately denied or discouraged in patient populations where it could be of benefit. Conversely, if risks are underestimated, then medical imaging may expose patient populations to radiation when there is little diagnostic benefit.

Due to increased utilization primarily of computed tomography (CT), ionizing radiation exposure to the general population from medical diagnostic imaging procedures is on the rise in the United States (Wiest *et al.* 2002; Fazel *et al.* 2009; NCRP 2009; Sodickson *et al.* 2009; Larson *et al.* 2011), and around the world (Shrimpton *et al.* 2006; Aroua *et al.* 2010; Etard *et al.* 2010; Tabeie *et al.* 2013). Medical doses now represent the largest source of population dose in the United States. The collective medical dose to the public has been increasing broadly, but at varying rates across different sectors of the population, with the largest growth rate occurring among older patients (Smith-Bindman *et al.* 2008; Fazel *et al.* 2009; Smith-Bindman *et al.* 2012).

The increasing population dose, combined with widely publicized instances of accidental patient overexposures (Bogdanich 2009; Zarembo 2009) and unjustified exposures (Oikarinen *et al.* 2009), has generated concern among the public, regulatory authorities (Bogdanich 2010; FDA 2010), and in the scientific community (Brenner and Hall 2007; The Joint Commission 2011). Increasing doses from diagnostic medical imaging among pediatric patients (Brenner *et al.* 2001a; Larson *et al.* 2011) has generated special concern. Adding to the public alarm, articles have recently appeared in the peer-reviewed scientific literature purporting to directly observe increased cancer risks among populations exposed to low radiation doses, and several other articles have been published predicting excess cancer incidence from diagnostic imaging. There is, however, disagreement on how to estimate radiation risks, and how these estimates should be communicated to patients and the public. The purpose of this paper is to critically examine the studies most frequently cited as provid-

ing direct evidence of carcinogenicity associated with doses characteristic of diagnostic imaging, and to consider the most prudent expression of current knowledge of radiation risks associated with diagnostic imaging from a public health perspective.

WHAT ARE THE RISKS OF DIAGNOSTIC IMAGING EXAMS?

As previously discussed (Ulsh 2012), radio-epidemiologic studies traditionally start with the null hypothesis that there is no association between exposure to ionizing radiation and cancer risk (Rothman and Greenland 1998). Should the evidence prove sufficient to reject the null hypothesis in favor of an alternative hypothesis (*e.g.* radiation exposure increases the incidence of cancer in linear proportion to dose), the alternative is accepted in place of the null. If a particular study fails to observe a statistically significant change in cancer risk associated with radiation dose, the null stands *i.e.* the study fails to support the hypothesis that radiation exposure is causally related to cancer risk. In the event that a radio-epidemiology study fails to observe increases in cancer risk, it is critically important that the following mistakes in interpretation be avoided:

1. It should not be concluded that there is absolutely no relationship between radiation exposure and cancer risk. It is well known that radiation is a weak carcinogen, and radio-epidemiology studies almost always struggle with the problem of lack of statistical power to detect a very small effect hypothetically associated with low radiation doses (Land 1980). Absence of evidence is not evidence of absence (UNSCEAR 2000; ICRP 2005).
2. It should not be concluded, based on the preceding argument, that it is prudent to simply assume some undetectably small risk exists in the absence of evidence to support such an assumption. In particular, such an assumption violates logical principals (Walton 1999) and the scientific method (Popper 1959) by inappropriately shifting the burden of proof from the alternative hypothesis [*e.g.* low doses of radiation increase cancer risk in linear proportion to dose, all the way down to zero dose, as predicted by the linear, no-threshold (LNT) theory], to the null hypothesis (low doses of radiation have no effect on cancer risk). The prudence, or lack thereof, of such an assumption as a matter of radiation protection policy has no bearing on the success or failure of the scientific hypotheses predicted by the LNT theory.

The acceptance or rejection of the LNT theory is also not dependent on the presentation of other, putatively superior, alternative hypotheses (*e.g.* hormesis, linear threshold models). In other words, it is inappropriate to argue, for example, that since there is no demonstrably superior model (a very debatable argument in itself), we might as well continue

to assume a LNT relationship. There is either statistically significant evidence of increases in cancer risk associated with low doses of radiation, or there is not, regardless of the success or failure of other alternative hypotheses. What radiation protection measures should be taken in the absence of evidence of increases in cancer risk from low radiation doses is an important and subjective question, and depends on many non-scientific factors including the public health and financial consequences of various courses of action. However, it is inappropriate for such subjective considerations to enter into the objective evaluation of the hypotheses predicted by the LNT as a scientific theory.

The linear, no-threshold model is recommended by many expert advisory bodies for setting radiation protection regulations (NCRP 2001; ICRP 2005; NRCNA 2005), but most of these same agencies explicitly recommend against using the LNT to predict risks for individual patients, or to predict future cancer increases from low doses multiplied by large populations. It has been argued that the LNT is the most suitable model for regulatory and public health policy applications (Martin 2005). Conversely it has also been argued that continued reliance on the LNT for radiation protection and risk assessment is unjustified (Cuttler 2009). Suffice it to say, there is no scientific consensus on this issue. In a 2002 random survey of American and European subscribers to the journal *Science*, a majority of the respondents believed a sublinear threshold model more accurately describes low-dose radiation risks than does the LNT (Jenkins-Smith *et al.* 2009), though a plurality favor radiation protection standards based on LNT (Silva *et al.* 2007). There remains significant debate about whether low doses in general (Brenner *et al.* 2003; Dauer *et al.* 2010; Ulsh 2010, 2012), and doses from diagnostic imaging in particular (Brenner and Elliston 2004; Brenner and Hall 2007; Scott *et al.* 2008; Jaffurs and Denny 2009; Laskey *et al.* 2010; Einstein 2012), increase cancer risk. There is considerable evidence of thresholds and adaptive/hormetic dose responses in radiation biological studies (Luckey 1980, 1991; Redpath 2006; Scott *et al.* 2008; Ait-Ali *et al.* 2010; Kuefner *et al.* 2010; Munley *et al.* 2011; Phan and Boreham 2011; Phan *et al.* 2012; Ma *et al.* 2013; Antosh *et al.* 2014). It has been specifically argued that this evidence implies that the risks associated with diagnostic imaging procedures are overestimated by the LNT (Redpath 2006).

Numerous professional societies and expert advisory bodies have recommended against quantitatively estimating risks from low doses of radiation (Table 1). For example, the Health Physics Society has concluded,

> "In accordance with current knowledge of radiation health risks, the Health Physics Society recommends against quantitative estimation of health risks below an individual dose of 5 rem in one year or a lifetime dose of 10 rem above that received from natural sources… Estimation

TABLE 1. Professional society and expert advisory body statements on risks of low radiation doses

Expert body/ professional society	Statement
American Association of Physicists in Medicine	"Discussion of risks related to radiation dose from medical imaging procedures should be accompanied by acknowledgement of the benefits of the procedures. Risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged. These predictions are harmful because they lead to sensationalistic articles in the public media that cause some patients and parents to refuse medical imaging procedures, placing them at substantial risk by not receiving the clinical benefits of the prescribed procedures" (AAPM 2011).
Australasian Radiation Protection Society	"There is insufficient epidemiological evidence to establish a dose-effect relationship for effective doses of less than a few tens of millisieverts in a year above the background level of exposure". "…no inference may be drawn concerning the risk to health or risk of fatality of an individual from an effective dose below 10 mSv in a year. For individual doses less than some tens of millisieverts in a year, risk inferences are unreliable and carry a large uncertainty that includes the possibility of zero risk". (ARPS 2008)
Health Physics Society	"In accordance with current knowledge of radiation health risks, the Health Physics Society recommends against quantitative estimation of health risks below an individual dose of 5 rem in one year or a lifetime dose of 10 rem above that received from natural sources. Doses from natural background radiation in the United States average about 0.3 rem per year. A dose of 5 rem will be accumulated in the first 17 years of life and about 25 rem in a lifetime of 80 years. Estimation of health risk associated with radiation doses that are of similar magnitude as those received from natural sources should be strictly qualitative and encompass a range of hypothetical health outcomes, including the possibility of no adverse health effects at such low levels". "There is substantial and convincing scientific evidence for health risks following high-dose exposures. However, below 5–10 rem (which includes occupational and environmental exposures), risks of health effects are either too small to be observed or are nonexistent" (HPS 2010).
International Commission on Radiation Protection	"Collective effective dose is an instrument for optimisation, for comparing radiological technologies and protection procedures. Collective effective dose is not intended as a tool for epidemiological studies, and it is inappropriate to use it in risk projections. This is because the assumptions implicit in the calculation of collective effective dose (*e.g.,* when applying the LNT model) conceal large biological and statistical uncertainties. Specifically, the computation of cancer deaths based on collective effective doses involving trivial exposures to large populations is not reasonable and should be avoided. Such computations based on collective effective dose were never intended, are biologically and statistically very uncertain, presuppose a number of caveats that tend not to be repeated when estimates are quoted out of context, and are an incorrect use of this protection quantity" (ICRP 2007).
Society for Pediatric Radiology	"To prevent misconceptions and public alarm, it is important to realize that the radiation used in CT scans has not been proven to cause cancer during a child's lifetime. The very small risk of cancer from radiation exposure is an estimate and is based on information and statistics that are debatable" (SPR 2001).
United Nations Scientific Committee on the Effects of Atomic Radiation	"In general, increases in the incidence of health effects in populations cannot be attributed reliably to chronic exposure to radiation at levels that are typical of the global average background levels of radiation. … the Scientific Committee does not recommend multiplying very low doses by large numbers of individuals to estimate numbers of radiation-induced health effects within a population exposed to incremental doses at levels equivalent to or lower than natural background levels" (UNSCEAR 2012)

> of health risk associated with radiation doses that are of similar magnitude as those received from natural sources should be strictly qualitative and encompass a range of hypothetical health outcomes, including the possibility of no adverse health effects at such low levels...below 5–10 rem (which includes occupational and environmental exposures), risks of health effects are either too small to be observed or are nonexistent" (HPS 2010).

Similarly, and more directly focused on doses from medical imaging, the American Association of Physicists in Medicine (AAPM) has stated,

> "Risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged. These predictions are harmful because they lead to sensationalistic articles in the public media that cause some patients and parents to refuse medical imaging procedures, placing them at substantial risk by not receiving the clinical benefits of the prescribed procedures" (AAPM 2011).

Nonetheless, several review and editorial articles have been published claiming that we now have direct evidence of carcinogenic risk from doses characteristic of medical imaging.

The typical adult dose from a chest CT exam series is approximately 7 mGy, and the typical dose from a CT head series (Figure 1) is approximately 2 mGy (Mettler *et al.* 2008a). The corresponding doses for pediatric patients are approximately 3.0 mGy for a body CT, and 3.7 mGy for a head CT [values estimated from effective dose data for youngest and smallest patients shown in (Huda and Vance 2007)]. Is it true that "we have now passed a watershed in our field where it is no longer tenable to claim that CT risks are ""too low to be detectable and may be non-existent"" (Brenner and Hall 2012)? The studies cited in support of this assertion include the Japanese atomic bomb survivors, the Oxford Study of Childhood Cancer (OSCC), and new epidemiologic studies conducted in Great Britain and in Australia, each of which is considered below.

LIFE-SPAN STUDY OF THE ATOMIC BOMB SURVIVORS

Some authors have claimed that the Life Span Study (LSS) of the Japanese atomic bomb survivors provides direct evidence of increased cancer risks in the range of doses typical of CT scans (Brenner *et al.* 2003; Hall 2003; Brenner and Hall 2012). Brenner and Hall (2012) cited the most recently published solid cancer incidence data (Preston *et al.* 2007)

FIGURE 1. A CT head scan.

and asserted "about 30,000 atomic bomb survivors who were located several miles from the bomb epicenter did indeed receive organ doses comparable with those from a few CT scans and did show a significant increase in cancer risk". Preston *et al.* (2007) stated,

> "Of the 105,000 members of the LSS included in the current analyses, about 35,000 received doses between 5 and 200 mGy. This large group of low- to moderate-dose survivors provides adequate statistical power to make direct inferences about cancer risks at low doses."

Elsewhere Brenner *et al.* (2003) pose the question, "What is the lowest dose of x- or γ-radiation for which convincing evidence of significantly elevated cancer risks in humans is available?" Do the atomic bomb survivor data really directly demonstrate significant excess risks in the range of typical CT exams? It is difficult to answer this question from Preston *et al.* (2007), because the authors never directly state the lowest dose where statistically significant increased risks are directly observed. They did state, "There was a statistically significant dose response in the range of 0–0.15 Gy", and they reported "The data were consistent with a linear dose response over the 0- to 2-Gy range". It is not entirely clear whether this can be interpreted to mean that the risks in the range of 0 to <0.15 Gy were *not* statistically significantly increased, but a visual inspection of

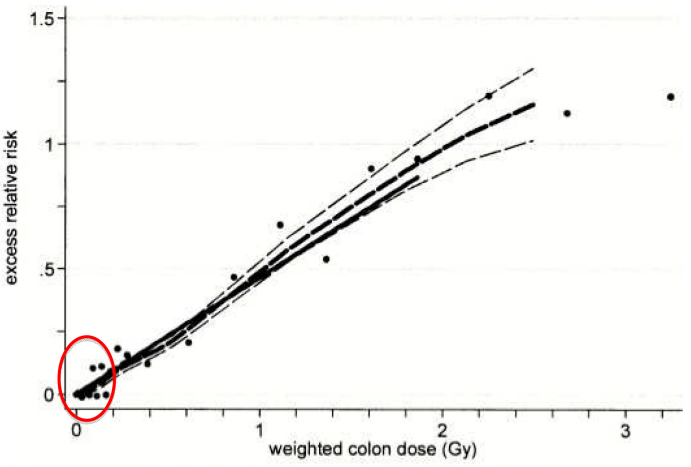

FIGURE 2. Excess relative risk (ERR) for all solid cancer incidence in relation to radiation exposure among the atomic bomb survivors, 1958-1998. The thick solid line is the fitted linear gender-averaged ERR dose response at age 70 after exposure at age 30 based on data in the 0- to 2-Gy dose range. The points are non-parametric estimates of the ERR in dose categories. The thick dashed line is a nonparametric smooth of the category-specific estimates and the thin dashed lines are one standard error above and below this smooth. Figure reproduced from (Preston *et al.* 2007) with permission. Red oval added to emphasize low dose region discussed in text.

their data (Figure 2) would appear to support such an interpretation. Although Preston *et al.* (2007) did not present confidence intervals on the individual ERR data points, their graph of the ERR for all solid cancer incidence reveals that several of the data points below 0.2 Gy have central estimate values that are approximately zero (Figure 2). If this interpretation is correct, and the ERR from zero to approximately <150 mGy are not statistically significantly elevated, it means that the LSS study does not support the assertion that even doses more than 20 times higher than an adult chest CT have been shown to be associated with increased cancer risks. This conclusion is consistent with assessments by the Health Physics Society (HPS 2010) and the American Association of Physicists in Medicine (AAPM 2011) (Table 1) which Drs. Brenner and Hall question (Hall 2003; Brenner and Hall 2012).

In support of the assertion that the LSS data show direct evidence of low dose risks, Hall (2002) presents a graph reportedly showing ERR for cancer mortality in A-bomb survivors from 1950-1990 over the range of 0 to approximately 150 mSv (his Figure 6). The point of Hall's figure, as described in the text, was to show,

> "radiation-induced cancer risk estimates are now available from individuals exposed over 50 years ago to doses comparable to those currently involved in helical CT. No theories, no extrapolations, no models are involved" (Hall 2002).

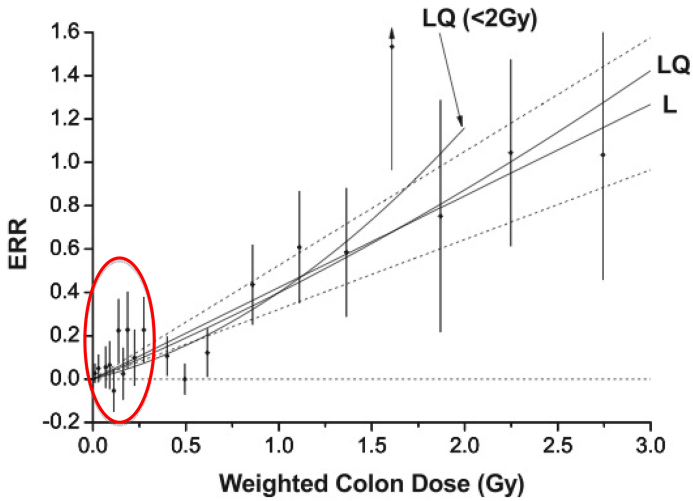

FIGURE 3. Excess relative risk (ERR) for all solid cancer mortality in relation to radiation exposure among the atomic bomb survivors, 1950-2003. The black circles represent ERR and 95% CI for the dose categories, together with trend estimates based on linear (L) with 95% CI (dotted lines) and linear-quadratic (LQ) models using the full dose range, and LQ model for the data restricted to dose <2 Gy. Figure reproduced from (Ozasa *et al.* 2012b) with permission. Red oval added to emphasize low dose region discussed in text.

The latest LSS mortality data contradict Hall's conclusion that this data directly demonstrate risks from low radiation doses. Figure 3 [which is reproduced from Figure 4 of (Ozasa *et al.* 2012b, 2012a)] shows the updated version of the mortality data considered by (Hall 2003). Four of the five lowest data points (over the same low dose range 0 to <150 mGy) have central estimates of excess relative risk slightly above zero and one has a central estimate below zero, but none of them are statistically significantly elevated. With no theories, no assumptions, and no extrapolations, cancer mortality risks from doses even more than 20 times higher than the typical adult chest CT exam are not statistically significantly elevated. This does not support the conclusion of Hall (2003) that the LSS data provide direct evidence of low-dose cancer risk. In fact, Ozasa *et al.* (2012b, 2012a) concluded "the estimated lowest dose range with a significant ERR for all solid cancer was 0 to 0.20 Gy". This means that even doses almost 30 times higher than the dose received from a typical adult chest CT exam series and approximately 100 times higher than the dose from a typical adult head CT series did not carry statistically significantly increased solid cancer risks. On this basis, claims that the atomic bomb survivor data provide direct evidence of increased cancer risks from doses in the range of a typical single, or even several, CT exams are not supported.

But there is more to the story. The latest LSS incidence and mortality data are also consistent with a nonzero dose threshold. Preston *et al.* (2007) state that the best estimate of a threshold is 0.04 Gy with an upper

90% confidence interval of 0.085 Gy. They note that the linear-threshold model was not statistically significantly superior to a linear no-threshold model, however they did not discuss whether the converse is also true (*i.e.* a linear model is not statistically significantly superior to a linear-threshold model). If neither model is statistically significantly superior to the other, then a proper interpretation is that the data are consistent with both models and the data are insufficient to exclude one model in favor of the other. With regard to the mortality data, Ozasa *et al.* (2012b) concluded that "a formal dose-threshold analysis indicated no threshold; *i.e.*, zero dose was the best estimate of the threshold". So is this the piece of atomic bomb survivor evidence that shows significant risks from doses typical of CT exams? A close look at how Ozasa *et al.* (2012b) conducted their threshold analysis reveals that the answer is again, no. According to Doss (2012, 2013), the functional form used by Ozasa *et al.* (2012b) allowed only positive values, but one of the data points had a negative central estimate value, and eight of the ten lowest dose data points had 95% confidence intervals that included negative values (Figure 3). Alternative analyses that did not use a functional form, but instead used the data to determine the shape of the fit, demonstrated that a nonzero threshold could not, in fact, be excluded.

Even after six decades studying the atomic bomb survivors, other important questions remain. In particular, both the latest mortality (Ozasa *et al.* 2012b) and incidence (Preston *et al.* 2007) data continue to assume a constant neutron relative biological effectiveness (RBE) value of 10. However, there is strong indication that this value is significantly underestimated, perhaps by as much as a factor of 10, both in the epidemiological data (Kellerer *et al.* 2006; Walsh 2013), and in chromosome aberration data (Sasaki *et al.* 2006; Sasaki *et al.* 2008).

This is not a trivial issue, as the evidence suggests that cancer risks could be reduced by a factor of 0.7 if a more appropriate neutron RBE value were adopted (Sasaki *et al.* 2008). A constant neutron RBE of 10 is not consistent with the latest ICRP guidance on the subject (ICRP 2003b), and use of the RBE values recommended by ICRP would result in a significant decrease in the risk estimate for gamma radiation (Ruhm and Walsh 2007). In addition, chromosome aberration data suggests that the neutron RBE is higher at lower neutron doses. This would induce more curvature in the dose-response – in other words, more departure from linearity. There is also evidence of curvature in the cancer mortality data (Walsh *et al.* 2004a), and it appears to be increasing with time (Ozasa *et al.* 2012b). Intuitively, this might suggest that the degree of risk overestimation in the current LSS reports is even more significant at lower doses. Some caution is in order here, as these conclusions are based on publicly available grouped LSS data. Confidence in these conclusions would be strengthened if they were based on analyses of individual LSS data (Ruhm and Walsh 2007).

In light of the neutron RBE issue, the LSS's use of the colon (a deep organ with a relatively high degree of neutron shielding by other tissues, compared to shallower organs) as a target organ for the combined all solid cancer category is especially problematic. In addition to the neutron RBE issue, there are very real differences in the etiology of cancers and radiosensitivity in different organs. For example, there is strong evidence of a relationship between high doses of radiation and cancers of the female breast, colon, esophagus, liver, lung, ovary, salivary gland, stomach, and urinary bladder, but there is no consistent evidence of a similar relationship for Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma or cancers of the gall bladder, larynx, male genitalia, oral cavity, pancreas, pharynx, prostate, skin (squamous cell carcinoma and malignant melanoma), small intestine, and uterus (Ulsh 2012). There is even evidence of differences between cancer types in the latest LSS cancer incidence data (Preston *et al.* 2007), where the reported excess relative risk values estimated at 1 Gy (assuming neutron RBE=10, and a LNT model) for cancers of the rectum, gallbladder, lung, non-melanoma skin, breast, uterus and "other" were significantly different than that reported for all solid cancers combined. Even when higher neutron RBE values are used, there are indications that there are differences between specific organ ERR estimates and the all solid cancer combined estimate, though the differences shrink as neutron RBE is increased (Walsh *et al.* 2004b). The obvious advantage of considering all solid cancers together is that it provides a larger number of cancer cases compared to any individual site, and therefore increases the putative statistical power to detect an effect. However, real differences in the types of cancers being combined would compromise the appropriateness of the all solid cancer combined category.

OXFORD STUDY OF CHILDHOOD CANCERS

Another study cited as providing direct evidence of increased carcinogenic risks in the range of doses typical of diagnostic imaging is the Oxford Study of Childhood Cancers (OSCC), which purported to have observed increased risks after cumulative doses as low as 10 mSv [(Doll and Wakeford 1997), but see also (Boice and Miller 1999)]. It has been claimed that, "the Oxford Study of Childhood Cancers was able to detect a significant increase in paediatric cancer risk for a mean dose of only 6 mGy" (Brenner 2014). In contrast to these plain, unreserved assertions, there is a great deal of debate about the OSCC. Some authors support the view that the OSCC provides evidence of increased carcinogenic risks from *in utero* exposures (Doll and Wakeford 1997), while others have raised serious questions about the study (Boice and Miller 1999; ICRP 2003a; Brent 2013).

The ICRP conducted a detailed analysis of the OSCC (ICRP 2003a). They made no claims that the OSCC provided direct and conclusive evidence of carcinogenic risks at very low doses. Indeed, they noted several weaknesses and limitations of the OSCC, including:

Selection biases

The OSCC studied only fatal cancers, while current standards of epidemiologic practice are to use incident cases so as to avoid possible biases from selection factors related to fatality. The ICRP noted "the potential for such biases probably increased with calendar time because treatment of childhood cancers, especially childhood leukaemia, has become more and more successful" (ICRP 2003a). The ICRP also noted the high losses of study subjects in the OSCC, and concluded "Study losses of this magnitude are generally considered to be unacceptable by present day standards for epidemiologic studies" (ICRP 2003a).

Information biases

The OSCC relied on interviews with mothers of pediatric study subjects conducted by doctors and nurses from local health departments to determine the number of x-ray exams subjects were exposed to *in utero*. In contrast, modern case-control studies use specially-trained interviewers. The interviewers were also most likely aware of the status of the interview subjects as cases or controls, which raises concerns about possible interviewer bias. There is evidence of this bias, as the ICRP stated, "In both of the OSCC methodological studies, the cases showed slightly more over-reporting and slightly less under-reporting of abdominal irradiation, which would produce a bias" (ICRP 2003a). There are serious questions about the accuracy of the interviewees' memory, and the ICRP concluded "… there may be substantial inaccuracy in reporting, and there is a suggestion in the OSCC study that differential recall of x-ray procedures could have biased the results", and "…only 66% of reported prenatal x rays were actually confirmed" (ICRP 2003a).

Uncertainties in dose estimates

There is significant uncertainty in the dose estimates used in the OSCC. Sources of this uncertainty include:

- reliance on medical personnel's memories when medical records did not indicate the number of films per x-ray exam (which was common pre-1960);
- despite the fact that a woman may have had multiple x-ray exams throughout her pregnancy, details of only the first exam were consid-

ered in the dose-response analysis in early reports, and later reports are unclear on how this issue was treated;
- fluoroscopic exams (which deliver very high doses relative to typical abdominal film x-rays) were not included in dose estimates;
- doses from non-abdominal x-rays were not included, in spite of the fact that these could deliver significant abdominal doses because the ovary was in the direct beam in over 50% of chest x-rays.

On the issue of uncertainty in dose estimates, the ICRP concluded,

> "…a major limitation of this dataset is the uncertainties about in-utero doses, as discussed in Chapter 3. Dose uncertainties have not been taken into account adequately by any investigator, and it seems unlikely that sufficient historical dosimetric data are available to characterise uncertainties or achieve more accurate dose estimates" (ICRP 2003a).

Comparison with other studies

Other studies of pediatric populations exposed to very low doses failed to observe increased risks (Hammer *et al.* 2009; Hammer *et al.* 2011). A systematic review of numerous other studies failed to find any associations (Schulze-Rath *et al.* 2008). Similarly, reviews of epidemiological studies of adult and pediatric populations exposed to medical diagnostic or therapeutic procedures found inconsistent results, with some studies reporting associations between number of procedures and subsequent cancer, and some studies failing to observe such associations (Ron 2003). Specific studies of pediatric populations more frequently reported positive dose-responses (Ron 2002). All of these studies examined planar and projection radiography studies, and while earlier protocols tended to result in higher doses relative to modern protocols, in general they all deliver significantly lower doses than CT exams. Another point that must be remembered is that these are studies of populations with underlying medical conditions, and the impact of these conditions on risk estimates must be considered before generalizing to the population at large.

The ICRP also noted a discrepancy between case-control studies (like the OSCC), which are subject to recall bias and some of which report significant increases in risk, and cohort studies which are not subject to recall bias, and which have consistently failed to observe increased risks. On this subject, the ICRP stated, "…most of the case–control studies in Table 8.5 had the potential for recall bias just as the OSCC study did" and "One notable feature of the data in Table 8.6 is the low RRs for cohort studies of in-utero diagnostic radiation effects" (ICRP 2003a). The ICRP noted that while the confidence intervals of risk estimates from cohort

studies are wide enough to be compatible with those of the OSCC, "the cohort studies provide limited evidence at best for increased risk associated with in-utero radiation exposure" (ICRP 2003a). Brent noted that of 35 case-control studies studying childhood cancer risks in children of women who received prenatal diagnostic x-ray exams, 25 of them failed to observe statistically significantly increased relative risks, and none of the 17 cohort studies of similar populations observed statistically significantly increased relative risks (Brent 2013).

Similarly, the ICRP compared the risk estimates of the OSCC with the results from the LSS studies, and noted, "Although the observed number of cancer deaths from in-utero irradiation and the number expected from the OSCC-based risk estimate may be marginally statistically compatible, the support for the OSCC-based risk projection is weak at best" (ICRP 2003a). They also stated, "By way of contrast, the in-utero risk estimate calculated from collective dose and person-years for the Japanese atomic bomb cohort (Section 8.8.4) yielded a negative risk estimate that is statistically incompatible with a positive association" (ICRP 2003a). It should be noted that since the ICRP published their analysis in 2003, a study of the solid cancer incidence in atomic bomb survivors exposed *in utero* has been published (Preston *et al.* 2008). That study concluded that in contrast to the OSCC, "The absolute risks among those [*atomic bomb survivors*] exposed in utero are therefore likely to be considerably lower than simple projections based on studies of childhood cancers in other in utero–exposed populations (which have been estimated to be approximately 6% per Sv by age 15 [*in the OSCC*]) and may be lower than absolute risks among those exposed early in life" (explanatory text in *italics* added). (Preston *et al.* 2008) did caution, "additional follow-up of this cohort is necessary before definitive conclusions can be made about the nature of the risks for those exposed in utero."

In contrast to other studies, the OSCC observed similar risks for hematopoietic cancers and for solid cancers, and it has been suggested that this may be a sign of bias (Boice and Miller 1999). The ICRP agreed, concluding, "Although the arguments fall short of being definitive because of the combination of biological and statistical uncertainties involved, they raise a serious question of whether the great consistency in elevated RRs, including embryonal tumours and lymphomas, may be due to biases in the OSCC study rather than a causal association"(ICRP 2003a).

In summary, the ICRP concluded, "there are several methodological weaknesses in the OSCC dataset" (ICRP 2003a). They stated that these weaknesses do not completely invalidate the study, but they may have a quantitative impact on the results. In light of these weaknesses and limitations, assertions that the OSCC provides incontrovertible direct evidence of carcinogenic risks from doses typical of medical imaging are overstated.

DO NEW EPIDEMIOLOGICAL STUDIES DIRECTLY OBSERVE RISKS?

It has been claimed that a recent study conducted in the UK (Pearce *et al.* 2012) is "the first epidemiological study to show an excess incidence of leukaemia and brain cancer in children and adolescents who had received CT scans", and "the new data confirm that the cancer risk associated with the radiation from a CT scan is very small, but not zero" (Hall and Brenner 2012). However, significant limitations of the (Pearce *et al.* 2012) study have been identified (Cohen 2013), including (1) individual doses were not directly assessed, but rather "typical" doses were assumed; (2) doses applied were for adults and assumed no decrease for pediatric patients, even though this is the standard of care; (3) the reason for the CT was not considered, and it is possible that the underlying condition indicating the CT has associated cancer susceptibility. One of the strongest associations (Pearce *et al.* 2012) observed was for gliomas, but they did not control for prior head injury. Head injuries are a common reason for head CT in children (Maguire *et al.* 2009), and head injury may be associated with brain tumors. Brenner and Hall cited a single study (Nygren *et al.* 2001) to assert that there were no obvious confounders for brain tumors. The single study Brenner and Hall cited failed to observe an association between prior traumatic head injury and primary brain tumors among more than 311,000 Swedish patients. But the possibility of confounding cannot be dismissed on the basis of one study. There is a very real possibility of reverse causation (*i.e.* an underlying medical condition associated with brain cancer may be the reason for the scan) (UNSCEAR 2013). The epidemiological evidence of an association between head injury and subsequent brain tumors is mixed (Inskip *et al.* 1995) with some studies reporting an association (Hochberg *et al.* 1984; Preston-Martin *et al.* 1989; Hu *et al.* 1998; Preston-Martin *et al.* 1998; Monteiro *et al.* 2006; Chen *et al.* 2012) and some not (Parker and Kernohan 1931; Choi *et al.* 1970; Annegers *et al.* 1979; Carpenter *et al.* 1987; Schlehofer *et al.* 1992; Zampieri *et al.* 1994; Inskip *et al.* 1998; Wrensch *et al.* 2000; Rutherford and Wlodarczyk 2009). But formal criteria for establishing causality between brain tumors and prior traumatic injury have been published (Salvati *et al.* 2004), and there are many confirmed case reports in the literature of gliomas forming at the exact location of a prior brain injury, often verified by CT or magnetic resonance imaging (MRI) (Schmitt 1983; Troost and Tulleken 1984; Di Trapani *et al.* 1996; Sabel *et al.* 1999; Henry and Rajshekhar 2000; Magnavita *et al.* 2003; Moorthy and Rajshekhar 2004; Salvati *et al.* 2004; Anselmi *et al.* 2006; Zhou and Liu 2010). This partial list of references is by no means meant to be exhaustive – it is simply intended to demonstrate that there are numerous examples of confirmed case reports relating gliomas to prior trauma. There are also several case reports between previous trauma and subsequent development of meningioma (Sakai *et al.* 1981; Rodrigues *et al.* 2006; Francois *et al.* 2010; Kizilay *et al.* 2010), which is another of the primary brain tumor types observed by

(Pearce *et al.* 2012). There is epidemiological evidence of this relationship as well, (Preston-Martin *et al.* 1998), including dose response relationships (Phillips *et al.* 2002). Past epidemiological evidence in large part shows an association between radiation exposure and brain tumors only after high doses characteristic of radiotherapy (UNSCEAR 2006; Mettler and Upton 2008). No consistent association has been evident at the low doses typical of modern diagnostic imaging. The possibility that the relationships observed by (Pearce *et al.* 2012) are a result of underlying medical conditions cannot be discounted in the absence of proper controls. For example, where CT scans were given to persons with head injuries, matching controls would have been persons with head injuries that did not receive CT scans. In light of this limitation, and the others described by (Cohen 2013), citation of this study in support of projections of increased numbers of cancer among the general population (Miglioretti *et al.* 2013), and as definitive vindication of prior controversial claims of cancer risks associated with CT (Brenner and Hall 2012) is unconvincing.

Similarly, the (Mathews *et al.* 2013) study has been characterized as "compelling data on the magnitude of the cancer risk attributable to ionizing radiation" from CT scans (Sodickson 2013). However several limitations in the Mathews *et al.* (2013) study have been identified (Walsh *et al.* 2013), including: (1) the misclassification of patients with unknown exposures at the start of the study as unexposed, which the authors assert would have a small impact, but no supporting evidence for this assertion was provided; (2) omission of doses from missed exams; (3) omission of doses from retakes. There are several puzzling results, including (1) dissimilarity in leukemia patters compared to the A-bomb survivors; (2) excess risks for all solid cancers except brain cancer in the first four years after exposure; (3) significant excesses of melanoma and Hodgkin's lymphoma, which is at odds with other more powerful studies; and (4) the lack of any excess breast cancer.

UNSCEAR recently reviewed the epidemiologic evidence on the sensitivity of pediatric subjects relative to adults (UNSCEAR 2013), and concluded:

- For 25% of the cancer types, children appear to be more sensitive than adults;
- Children appear to have the same radiosensitivity as adults for 15% of cancer types;
- For 10% of the cancer types, children appear to be less sensitive than adults;
- For 20% of cancer types, no conclusion can be drawn about the sensitivity of children relative to adults because the evidence is too weak; and
- For about 30% of cancer types there is only a weak relationship or no relationship at all to radiation exposure.

NEW ARTICLES – PREDICTING EXCESS CANCER INCIDENCE

It is obvious that the advice of numerous professional societies and expert advisory bodies against multiplying very low doses by large populations to estimate radiation-induced health effects using the LNT (Table 1) is frequently contravened even in the scientific literature (Pauwels and Bourguignon 2011). Much of the public alarm regarding doses from diagnostic imaging procedures has been the result of newspaper articles and articles in the scientific literature predicting excess radiation-induced cancers from these procedures. These studies are frequently based on LNT calculations of risk. There are numerous examples of these kinds of articles generating the sensational claims the AAPM warned against.

An article in the January 30, 2014 edition of *the New York Times* was alarmingly titled, "We Are Giving Ourselves Cancer", and was accompanied by a provocative cartoon of a doctor holding an x-ray film, and wearing a gas mask and military helmet (Redberg and Smith-Bindman 2014). The authors only mentioned in passing that medical imaging saves lives, and quickly moved on to the many sensational claims asserting that CT scans are killing patients that formed the main message of the article. Readers were provided no balancing perspective, and no indication that the claims in this article were far outside the scientific mainstream.

Another well-known example was a paper appearing in the American Journal of Roentgenology (AJR) in 2001 which predicted an increase in cancer from CT scans in pediatric patients (Brenner *et al.* 2001a). This paper garnered an enormous amount of attention in the popular press, including an article in *USA Today* (Sternberg 2001), which generated public alarm about the doses and putative risks associated with imaging. The AJR paper multiplied the low estimated doses from CT scans in pediatric patients by population CT utilization data and risk estimates derived from the Japanese atomic bomb survivors to predict an excess of cancer deaths in US children. In this instance, even though the original AJR paper discussed uncertainties associated with the excess cancer predictions, the *USA Today* article omitted any mention of uncertainties, and stated "Each year, about 1.6 million children in the USA get CT scans to the head and abdomen — and about 1,500 of those will die later in life of radiation-induced cancer" (Sternberg 2001). The *USA Today* article was severely criticized in the scientific literature as grossly sensational and a misrepresentation of the AJR paper (Donnelly and Frush 2001; Sane 2001). However the authors of the AJR paper have described the press coverage (including the *USA Today* article) as "quite responsible" (Brenner *et al.* 2001b) and "reasonably balanced reporting" (Brenner *et al.* 2001c). The Society of Pediatric Radiology (SPR) apparently disagreed, stating, "…the SPR considers the recent press coverage to be unbalanced and potentially dangerous to the health and welfare of children" (SPR 2001). The SPR also stated,

> "To prevent misconceptions and public alarm, it is important to realize that the radiation used in CT scans has not been proven to cause cancer during a child's lifetime. The very small risk of cancer from radiation exposure is an estimate and is based on information and statistics that are debatable" (SPR 2001).

The SPR's position has also been explicitly criticized (Brenner *et al.* 2001c). Brenner *et al.* (2001c) asserted "small individual cancer risk must be multiplied by a large (and increasing) population of children undergoing CT examination…" to gain a public health perspective, and further, "even a very small individual radiation risk, when multiplied by such a large (and increasing) number of children, is likely to produce a significant long-term public-health issue." These statements are in direct contradiction to the advice offered by the The American Association of Physicists in Medicine, the Australasian Radiation Protection Society, the French Academies of Science and Medicine, the Health Physics Society, the ICRP, the International Organization for Medical Physics, the Society for Pediatric Radiology, and UNSCEAR, (Table 1). Such predictions frighten the public away from medically indicated exams (Boutis *et al.* 2013; Fletcher *et al.* 2013), and on that basis are damaging to public health. Almost 35 years ago, Lauriston Taylor, past president of the Health Physics Society and the first Chairman of the National Council on Radiation Protection & Measurements (NCRP), condemned this practice, stating:

> "An equally mischievous use of the numbers game is that of calculating the number of people who will die as a result of having been subjected to diagnostic X-ray procedures. An example of such calculations are those based on a literal application of the linear, non-threshold, dose-effect relationship, treating the concept as a fact rather than a theory. ... These are deeply immoral uses of our scientific knowledge." (Taylor 1980)

In yet another example, another study used risk estimates provided by the Biological Effects of Ionizing Radiation (BEIR) VII Committee (NRCNA 2005), combined with preliminary population CT utilization data used by the NCRP (Mettler *et al.* 2008b), to project an additional 29,000 cancers in the US population per year (Berrington de Gonzalez *et al.* 2009). A similar, frequently cited study examined the frequency of 11 common CT exams among 1119 patients at San Francisco area medical facilities, estimated the effective doses of the exams, multiplied by BEIR VII risk coefficients, and concluded, "An estimated 1 in 270 women who underwent CT coronary angiography at age 40 years will develop cancer from that CT scan (1 in 600 men)" (Smith-Bindman *et al.* 2009). A more cautiously worded study of CT coronary angiography calculated radiation

risks from this procedure, but also discussed limitations (including the application LNT as recommended by BEIR VII) at some length (Einstein *et al.* 2007). Another recent study has predicted that the 4 million pediatric CT scans performed in the US each year will eventually result in 4870 future cancers (Miglioretti *et al.* 2013). Similarly, it has been predicted that radiogenic cancers from diagnostic imaging will account for 0.6 to 3% of total cancers in 15 countries around the world (Berrington de Gonzalez and Darby 2004). Excess cancers in specific populations at a sub-national level have also been predicted using similar methodologies, and the predicted excesses are usually in the range of a few percent of total expected cancers (Sodickson *et al.* 2009; Dijkstra *et al.* 2010; Khong *et al.* 2013).

These projections calculate theoretical, rather than empirically observed, risks (NRCNA 2012) and such estimates have been criticized on a number of bases, including inappropriate averaging of doses received by a segment of the population (*e.g.* medical patients receiving CT) over the entire population (McCollough *et al.* 2009; Pauwels and Bourguignon 2011). In doing so, they assume that the population being scanned has the same risk profile as the population at large. There is evidence that this is incorrect, and in fact, the fraction of the population undergoing, for example CT scans, is at significantly higher risk of death, presumably from their underlying medical conditions (Zondervan *et al.* 2011). Failure to take this into account can result in significant overestimates of radiation risk (Brenner *et al.* 2011). In addition, these studies have been criticized for frequently using effective dose (designed for radiological protection purposes) for risk estimation (for which effective dose is inappropriate), and for applying risks calculated for Japanese atomic bomb survivors to an American public exposed to fractionated medical exposures, often with underlying medical conditions, using the LNT hypothesis (Hendee and O'Connor 2012).

There are real public health consequences of these sensational predictions. A recent study observed that when parents of children presenting with isolated head injuries in an emergency department were advised that a CT scan was indicated, but may increase their child's risk of cancer by 1 in 10,000 [based on (Pearce *et al.* 2012)], willingness to proceed with the scan was reduced by over 20% (Boutis *et al.* 2013). There is also anecdotal evidence from professionals in the imaging field that articles in the popular press about radiation risks from medical imaging are generating concern among patients (Esz 2013; Fletcher *et al.* 2013).

REAL BENEFITS VS. HYPOTHETICAL RISKS

It is important to clarify that none of the analyses provided in this paper prove an absolute absence of risks from CT exams. Absence of evidence is not the same as evidence of absence. However absence of evidence cer-

tainly should not be interpreted as evidence of increased risks either (Ulsh 2012). To be consistent with the logical underpinnings of the scientific method, the burden of proof must be born by those asserting an effect (Walton 1999; Ulsh 2012). It is frequently argued that it is prudent to assume some small risk from low radiation doses, even if it cannot be directly demonstrated (ICRP 2007). This argument would only be compelling if there was no economic, or more importantly, public health cost of assuming an undetectable risk. This is certainly not the case for medical imaging. Assuming a risk where none can be demonstrated frightens patients and parents away from medically indicated exams (Boutis *et al.* 2013), and distorts the justification process. This entails real public health costs.

So what are physicians to do? What advice should they offer their patients on diagnostic medical imaging? The following recommendations have been offered for ordering physicians (Huda 2009):

Only tests that will affect patient management should be ordered

This case can be made on the basis of most productively allocating limited resources – there is no need to resort to exaggerated estimates of risks which distort the justification process.

Non-ionizing imaging modalities should be considered, especially for pediatric patients

This just makes sense in the interest of prudence, as long as the same information can be obtained with non-ionizing modalities (Muratore 2012). However, a consideration of the very real risks of non-ionizing imaging modalities (*e.g.* sedation, often required for MRI in young children) must be a part of this decision (Brody and Guillerman 2014).

Tests should only be ordered where there are potential patient benefits

Again, this case can be made on the basis of most productively allocating limited resources.

Optimize radiation doses to be as low as reasonably achievable while maintaining diagnostic value

As explained by McCollough, "It's analogous to taking an aspirin. Taking a whole bottle all at once is risky, but taking two pills isn't. Still, if only one pill will get rid of my headache, I'll use just one. The radiation exposure from a CT scan isn't dangerous, but if we can use an even lower amount, without compromising the exam, that's what we'll do" (Mayo Clinic 2013). However, we must also be mindful of sacrificing diagnostic utility in the interest of reducing doses for which the risk is already too small to detect or nonexistent. As pointed out by (Brody and Guillerman 2014), dose minimization is not the same as diagnostic optimization, and the two can conflict.

The scientific and medical communities have too often been caught flat-footed by sensational claims of future cancers which frighten the public. As Sir Winston Churchill once famously said, "A lie gets halfway around the world before the truth has a chance to get its pants on". The time for timid and heavily caveated responses to these dangerous claims is well past. The message we should be sending to the public is that while trivial risks cannot be absolutely excluded, the best evidence we have fails to indicate any significant risks from the low doses associated with medical imaging (Ulsh 2010). Any risks that are so small that we cannot detect them are hypothetical, but the benefits of medical imaging are real and substantial. It is time to speak out forcefully and directly about the safety and real benefits of diagnostic medical imaging.

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