The Risk of Cancer after Computed Tomography in Pediatric Patients, a

Systematic Review.

By Sinisa Haberle

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Advisor  ________________

Dr. Lynn Fordham

Second Reader  ________________

Dr. Daniel Jonas

Date
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INTRODUCTION

CTs AND THEIR USE IN MODERN MEDICINE

The discovery of computed tomography (CT) has had a dramatic effect on the field of medicine and has revolutionized diagnostic radiology. Since it was initially discovered in the 1970s its use has steadily increased; the advent of multiphase (e.g. arterial and venous) scanning has further lead to an increase in the use of CT and an increase in radiation dose that is inherent in this new modality. The 3-dimensional views that CT can produce allow radiologists and physicians to more accurately diagnose diseases. The Department of Health and Human Services has estimated that over 62 million CT scans are currently obtained in the United States every year, including at least 4 million on pediatric patients.¹

CT scans were initially used for symptomatic patients where they were used as diagnostic tools; more recently whole body CT scans, CT colonoscopy, and CT of the chest are being used as screening modalities in the adult population.¹ Some of these areas, such as the whole body or lung cancer screening which are not indicated or recommended, are consumer-driven. The use of screening CT may not necessarily be harmful, if used appropriately, especially if it detects disease at an earlier and more treatable state. In some Dutch and Swedish centers CT is being used as a way to follow deterioration in Cystic Fibrosis patients.² This may be a reasonable use of CT since it is less invasive than bronchoscopy and the associated anesthesia. One can see that there has been a clear increase in CT use in medical practice.³ Some of this use has greatly benefited diagnostic capabilities; but there is still a great deal of overuse, as seen by the explosion in CT use over the past decade, which could potentially harm patients.³,⁴
Physicians and families of the patients continue to push for diagnostic certainty and it is hard to quantify what affect this has had on the utilization of CT use. With the increased use of CT scans comes increasing radiation exposure which has the potential to cause harm, most importantly cancer. The fact that pediatric patients are more radiosensitive than adults is why the increase in pediatric diagnostic use of CT is particularly worrisome. This issue has garnered increased national attention from the health care professionals who are involved in the care of pediatric patients.

THE USE OF PEDIATRIC CT

There has been a dramatic rise in the use of CT in the pediatric population over the past year, much more than in the adult population. A recent study found that from 2000-2006 head CT increased 23%, cervical spine CT by 366%, chest CT by 435%, abdominal CT by 49%, and miscellaneous CT by 96%. The study focused only on pediatric (0-17 years) population seen at a tertiary care emergency department (ED). These increases occurred despite an increase in pediatric ED volume by a mere 2% and stable triage acuity. Other authors have reiterated the same conclusion. One study of adult and pediatric patients showed that although CT accounts for approximately 10% of diagnostic procedures in large US hospitals, it accounts for approximately 65% of the effective radiation dose from all medical x-ray examination. What is even more worrisome is the fact that 30% of the patients undergoing CT have at least 3 scans, 7% have at least 5, and 4% have at least 9. Nevertheless, there are many patients who benefit from serial CT to monitor the progression or resolution of disease. In these patients serial CT exams are not only appropriate but also necessary.

There are many reasons for the increasing use of CT in pediatric patients. First, newer CT scans can develop images in less than 1 second, therefore eliminating the need for sedation to
prevent the child from moving during image capture. Second, there has been an increase in its use for pre-surgical planning such as in diagnosis of appendicitis. Third, the use of CT may also have increased due to the litigious concerns of practitioners. Fourth, because of the lack of communication, unnecessary CT scans are repeated as the patient passes between one medical system and another. Finally, CT is being used for new application such as CT enteroclysis and for monitoring of progression of CF disease.

A recent study looked at the process of clearing cervical spines, among the general population, in hospital ED settings. The authors state that defensive medicine complicates the process of clearing a patient’s cervical spine. The authors performed a review of literature that focused on cases of missed cervical injury. They concluded that almost all of the cases of Type I and Type III errors could have been avoided by ordering CT scans. Type I errors occur when inadequate or inappropriate tests were ordered and Type III errors occur when adequate tests were ordered and interpreted but when the test was not sensitive enough. The authors found that, on average, the missed cases were awarded $2.9 million dollars through law suits. The authors conclude that “exposure to significant liability suggests that a low threshold for computed tomography is a reasonable alternative”. Unfortunately, the authors never mentioned the cost of the radiation risk and the harms from CT scanning. Consequences of spinal cord injury are devastating especially in children who have their whole life in front of them. Therefore, presumably defensive medicine is more clearly seen in the care of pediatric patients seen in the ED; their care is always sensitive considering parental involvement. Similarly, another study of general trauma population concluded that obtaining a CT scan is justified on a cost-benefit analysis. The authors state that CT costs on average $328.93 while the cost of litigation is estimated to be around $500,000. Like in the previous paper, these authors also do not mention
the risks of radiation from CT scans. Both sets of authors concluded that from a cost perspective CT is the preferred approach in a trauma setting. Unfortunately, between 19-34% of all spinal cord injuries in children are spinal cord injury without radiological abnormality (SCIWORA). In these cases MRI would show the significant abnormality and therefore CT would not be the most appropriate imaging modality.14 These papers show that the litigious nature of our health care system supports the practice of defensive medicine and that we are not properly educated about the potential harms of radiation. Litigation, or the fear from litigation, adds to the cost of health care and burdens a system that already leaves 50 million people uninsured.

Many investigators have explored the radiological evaluation for appendicitis and whether CT is better than ultrasonography (US).15,16 CT has not lead to the decrease in negative appendectomy rate as had been initially hypothesized.17 Furthermore, pre-operative CT does not increase the accuracy of diagnosing appendicitis when compared with patients diagnosed with history, physical exam, and laboratory studies.15 US is cheaper and does not lead to radiation exposure when compared with CT. Many would argue that imaging delays the time to the operating room when physical exam has already made the diagnosis. A recent study evaluated the impact of imaging on evaluation, management, and outcome of pediatric patients who underwent appendectomy.18 The authors concluded that imaged patients experienced a significant delay in getting to the operating room (12.1 vs. 5.4 hours in non imaged patients) and incur 26% more cost while not receiving a clear outcome benefit.

The increase in CT use is a very important issue since the harms attributable to CT scanning are not yet directly known. CT is a great diagnostic tool but until recently people have not begun to talk about the effects of the radiation exposure that is a part of the exam. Children are much more susceptible to the harmful ionizing radiation because of the increased number of
dividing cells and because of their longer life expectancy.\textsuperscript{9} Therefore, the odds of developing cancer may be higher due to the increased lead time that is needed to express radiation induced cancer.\textsuperscript{19} In addition, Paterson et al. showed that tube current, which is a source of the radiation, is not adjusted on the basis of the patient’s age group and size. Therefore, they suggest that we are unnecessarily overexposing patients because of the CT parameters.\textsuperscript{20}

**BIOLOGICAL EFFECT OF LOW DOSES OF IONIZING RADIATION**

Ionizing radiation, such as that emitted by x-ray and CT, has by definition enough energy to remove electrons from their orbitals. In human bodies, hydroxyl radicals are formed from the interaction of water particles and ionizing radiation. These radicals can lead to double-strand breaks or base damage; ionizing radiation can also directly damage DNA.\textsuperscript{1} The human body constantly repairs damage that is caused by ambient radiation and other mechanisms but double-strand breaks are harder to repair. When these double-strand breaks are not repaired by natural defenses we develop point mutations, chromosomal translocations, and gene fusions.\textsuperscript{1} These processes can all lead to the induction of cancer that can have a lead time on the order of decades.\textsuperscript{21}

Much of the information that we have about the harmful effects of low dose radiation comes from the atomic bombs survivors in Japan.\textsuperscript{22} The data from these cohorts are used to predict radiation related risks from CT scans. In order to effectively evaluate radiation related risks investigators would have to conduct a large epidemiological study of millions of people and follow these people for three to four decades. It is hypothesized that this long lead time is needed for radiation induced cancers to be expressed.\textsuperscript{9} This is precisely why many of the studies have predicted the incidence of cancer from radiation by comparing their data with those of the Japanese cohort. A long term study of cancer incidence, directly caused by CT scans, would cost
millions of dollars, take several decades, and have to include hundreds of thousands if not millions of cases to show a risk increase from 0.2000 (which is the 1 in 5 risk in the general population) to a 0.2002 (which includes the general population risk plus the additional estimated 1 in 5000 risk from CT scans). Such a prospective cohort study could be performed in a setting of universal health care where health care records can be easily obtained from a centralized system. This would allow for a proper ascertainment of the exposure (CT scan) and the outcome of interest (cancer incidence or mortality). Therefore, recall bias would be eliminated as people would not have to remember whether they had a CT scan and more importantly the actual number of scans. People can have a single CT procedure but have multiple phases performed which leads to even more radiation exposure.

At the present time extrapolating data from the Japanese atomic bomb survivors is what the scientific community has to rely on. There is still a lot of uncertainty and only in the recent decade has there been a serious awareness about the side effects of CT use in pediatric population. This field of research will continue to grow and will hopefully provide some of the answers needed to guide further policy. Furthermore, as the initial CT “cohort” gets older we will be able to more accurately quantify the effect of CT on cancer incidence. Perhaps, a retrospective cohort study could be used to answer this question.

On an individual basis there is much agreement about a favorable benefit to risk ratio in most cases. Unfortunately, there are many cases where children are needlessly exposed to unnecessary CT scans. Furthermore, as a whole four million annual CT scans can lead to an increasingly important public health issue if there is an increased cancer risk. The increase in dialogue has already led to many changes in pediatric scan parameters and more judicious CT scan use.
The aim of this paper is to conduct a systematic review to answer the question of whether CT scans lead to an increased risk of cancer in the pediatric population. If there are no direct studies investigating the impact of pediatric CT cancer risk, this study aims to determine what other evidence from past radiation exposure can be used to estimate this risk of cancer from CT scans in the pediatric population. I will attempt to answer this question by doing a systematic review of the literature focusing on studies looking at the effects of CT scans on cancer risk; I will also look at the papers that focus on the estimated effects of CT use on cancer in pediatric patients if there is no data that directly links CT scans and cancer. Finally, I will try to state what we can do to minimize the exposure risk and what has already been done. One of the main barriers to more appropriate CT use is the lack of physician knowledge (ER, pediatricians, surgeons, and radiologists) about the radiation dose that a typical CT scan emits. The true risks, if there are any, from CT use will only be seen in the future when these children become older.

METHODS

DATA SOURCES AND SELECTION

One of the key questions that this systematic review aims to answer is whether CT can lead to an increased risk of cancer. In case the first question can not be answered, the second question tries to determine if there is any other evidence from past radiation exposure that can be used to estimate the risk of cancer from CT scans in pediatric patients. Here are included the articles that reported a cancer incidence or mortality associated with CT use specifically looking at pediatric patients. Other articles that looked at any other kind of radiation exposure were excluded from this review.
To identify articles that were relevant to the two key questions that I pose for this systematic review, I performed a search of literature in the MEDLINE database from July 1963 to January 12, 2008. The search focused on children and adolescents who underwent CT scans and their risk of cancer; in addition, I focused on papers that investigated this relationship by estimating cancer risk from prior epidemiological studies. I performed the search by typing in key words including computed tomography, tomography, child, infant, adolescent, neoplasm, cancer, and radiation induced. The articles were limited by the English language and by the studies performed on humans. I divided articles that did not directly relate to the first key question into six categories: incidence of cancer after Chernobyl, Japanese atomic bombs, and in the vicinity of nuclear plants, cancer after prolonged UV radiation exposure, and secondary cancer after childhood radiation of primary cancer. I excluded these articles because I wanted to have as direct link between CT radiation and cancer risk as possible. Another major category was opinion pieces about CT dose adjustment for pediatric patients. Excluding these papers, based on their titles, I reviewed the abstracts of 79 papers that focused on radiation and cancer risk. Majority (n=73) of these studies were excluded after reading the abstracts. These papers were excluded because the papers focused either on x-ray radiation or ionizing radiation form sources other than CT scans.
Figure 1: Decision Tree showing inclusion and exclusion of the studies identified

The remaining 6 studies were read in full. The eligibility criteria for inclusion of the remaining articles were that they estimated, using similar models, the risk of cancer from CT scans in pediatric patients. The remaining studies all estimated the outcome of interest which was the risk of cancer; they based their estimates by extrapolating models from Japanese atomic bomb survivors. These studies were included since they estimated a cancer risk that was specifically related to Computed Tomography. I reviewed the reference lists of these papers as well as other narrative reviews but did not find any other papers that looked at this specific topic.

DATA EXTRACTION AND QUALITY

I extracted data from the six studies of the estimates of cancer from pediatric CT use. The extracted data included the estimated cancer rates and the models used to come up with these rates. Data were assessed as of good, fair, or poor quality based on their use of accurate and
reasonable substitutions of standard CT radiation dose in their models and based on the models that they used when determining risk. Studies such as this have never been systematically critiqued; here I am presenting my quality assignment. A quality score of “good” was given to studies that used appropriate CT settings (in terms of mAs) used in typical pediatric radiological CT scans and based on the appropriate methodology. Methodology was graded based on whether the researchers calculated a dose that was distributed only to the exposed organs versus uniformly to the whole body. Also, it is important that different risk estimates were given based on the age and sex of the exposed patients so that a given dose posed a different risk for younger vs. older and for females vs. males. When studies applied a uniform dose to the whole body a quality rating of “poor” was applied. Studies that used mAs settings that are significantly higher than current practice received a “fair” rating as long as the methodology of their estimate was appropriate. The reason for not giving these studies a “poor” grade is based on the data that shows that some children are still being exposed to adult CT parameters, receiving higher doses than they should.20

DATA SYNTHESIS

Due to the nature of the question and because of the design of the included studies, I focused herein on the qualitative description of the studies, their results, the models that they used, and their limitations.
RESULTS

Due to the nature of the research question (CT radiation and cancer) a vast majority of the articles were unrelated to the topic being studied by this systematic review. As mentioned in the methods section they fit into one of six categories: incidence of cancer after Chernobyl, Japanese atomic bombs, and from the vicinity of the nuclear plants, cancer after prolonged UV radiation exposure, and secondary cancer after childhood radiation of primary cancer. Another major category was opinion pieces about CT dose adjustment for pediatric patients

Key question 1: IS THERE DIRECT EVIDENCE THAT PEDIATRIC CT CAN LEAD TO DEVELOPMENT OF CANCER IN PEDIATRIC PATIENTS?

Summery of Findings:

There are no studies directly addressing the link between CT exposure and cancer in pediatric patients.

Key Question 2: IF THERE IS NO DIRECT EVIDENCE, IS THERE ANY OTHER EVIDENCE FROM PAST RADIATION EXPOSURE THAT CAN BE USED TO ESTIMATE THE RISK OF CANCER FROM CT SCANS IN PEDIATRIC PATIENTS?

Summery of Findings:

Six studies met inclusion criteria for this question (Table 1).

**Table 1**: The estimated risks of cancer from pediatric CT scans. All of these studies are narrative reviews with modeling of cancer risks using appropriate methodology.

<table>
<thead>
<tr>
<th>Author and year published</th>
<th>Exposure Settings</th>
<th>Outcome</th>
<th>Methods</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brenner et al., 2001</td>
<td>404 mAs (Abdominal CT)</td>
<td>0.18% and 0.07% excess mortality from Abdominal and Head CT respectively in a 1 year old. For one year of CT scanning, for children under 15, there</td>
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<tr>
<td></td>
<td>462 mAs (Head CT) Based on one CT scan</td>
<td>Estimated the dose to each organ as a function of age, gender, and type of CT. Next they applied estimates for age, gender, and</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Source</td>
<td>Protocol Details</td>
<td>Organ Specific Risk per Unit Dose</td>
<td>Risk Estimation Methodology</td>
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<tr>
<td><strong>Brenner, 2002</strong></td>
<td>200 mAs (for both Head and Abdominal CT) Based on one CT scan</td>
<td>0.13% and 0.04% excess mortality from Abdominal and Head CT respectively.</td>
<td>Estimated the dose to each organ as a function of age, gender, and type of CT. Next they applied estimates for age, gender, and organ specific risk per unit dose.</td>
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<tr>
<td><strong>De Jong et al., 2005</strong></td>
<td>160 mAs 120 mAs if under 9 yrs Number of scans dependent on various models that changed median age of survival and the interval for scanning</td>
<td>2% mortality from CT induced cancer if median age of survival is 32. Increased to 13% mortality if median age of survival is 50. Five other models that looked at different CT settings and interval of scanning.</td>
<td>Assumed that a lung CT delivers a uniform dose to the whole body. They applied these dose estimates (1 mSv) to a risk model for all solid cancers.</td>
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<tr>
<td><strong>De Gonzalez et al., 2007</strong></td>
<td>160 mAs 120 mAs if under 9 yrs Number of scans dependent on various models that changed median age of survival and the interval for scanning</td>
<td>0.02% and 0.07% risk of radiation induced cancer for males and females assuming a median age of survival of 36. 0.08% and 0.46% risk of radiation induced cancer for males and females assuming a median age of survival of 50.</td>
<td>Used organ specific radiation doses (0.98 mSv for females and 0.82 mSv for males) and then applied these doses to radiation risk models for sex and organ specific cancer incidence developed by BEIR VII report. Furthermore, they applied these risks to organs that are specifically exposed to CT scans.</td>
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<td><strong>Huda, 2007</strong></td>
<td>20 mAs Based on one CT scan</td>
<td>Incidence of radiation induced cancer is 1.5/10,000 with half of these being fatal. 0.075% mortality from CT scanning</td>
<td>Calculated a dose of 0.55 mSv based on the proposed CF protocol. Used a patient effective dose that was the sum of the individual organs exposed and their risk.</td>
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specific radiosensitivities. Then they applied these doses to radiation risk models for sex and organ specific cancer incidence as developed by the BEIR VII report.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose Parameters</th>
<th>Methodology</th>
<th>Risk Estimate</th>
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<tbody>
<tr>
<td>Chodick et al, 2007</td>
<td>404 mAs (Abdominal CT) 462 mAs (Head CT) Based on one CT scan</td>
<td>Based on 17,686 yearly CT scans there will 9.45 cancer deaths from CT scans. Excess mortality of 0.29% in pediatric patients (less than 18 years) after one year of CT scans.</td>
<td>Estimated the dose to each organ as a function of age, gender, and type of CT. Next they applied estimates for age, gender, and organ specific risk per unit dose. Fair</td>
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The data reviewed show that there may be a small, yet not insignificant, risk of cancer in patients undergoing CT scans. All six of the articles developed methods for their estimates using the linear no-threshold model for estimating radiation risk from low dose radiation. This model states that the response to radiation is linear and that there is no safe level of radiation (no threshold); therefore the risk of cancer is directly proportional to the effective dose and this is the case at both high and low dose levels.

The estimates vary from study to study but all show a consistent increase in cancer mortality or incidence. Two of the studies looked at screening in CF patients and therefore these children were exposed to multiple CT scans. One study calculated an excess risk of cancer mortality for 1 year of CT scanning in the pediatric population. Four of the six studies estimated cancer risk based on a single CT scan; two of these studies also estimated an excess risk of cancer over the background rates of cancer for one year of CT scanning of the pediatric
population. Herein, I will explain the methods used by these researchers and will show how each group arrived at their results.

The initial piece of writing that looked at this issue was in the Brenner et al paper. Brenner et al estimated lifetime cancer mortality risks attributable to the radiation exposure from a single CT in a 1-year old to be 0.18% (abdominal CT) and 0.07% (head CT). Furthermore, based on 600,000 annual abdominal and head CT examinations performed on children younger than 15, they estimated that 500 will die from cancer attributable to radiation. Based on the estimate that 140,000 people from this cohort will ultimately die from cancer, the authors state that this will lead to a ~0.35% excess mortality risk. Their basic method used to estimate cancer mortality was to multiply age-dependent lifetime cancer mortality risks (per unit dose) by the estimated age-dependent doses produced by various CT exams. Furthermore, CT exposes the body to a non-homogeneous dose, and therefore risks have to be calculated based on the site-dependent risks. This takes into account that some organs, such as thyroid, digestive tract, and breasts are more sensitive to radiation than others and therefore the authors applied specific weighted factors to calculate the effective dose. For that reason the authors estimated the dose for each organ as a function of age, gender, and the type of CT scan. These organ-specific risks are summed together to yield the overall age-dependent lifetime cancer mortality risk. Authors used age-dependent doses from a 1989 survey of CT practices in Britain and scaled them to children using relative effective doses. The mean scan parameters were 404 mAs for abdominal CT and 462 mAs for head CT. They broke down their results further based on head and abdominal CT, risks to different organs, and differences in male and female risks. Brenner et al used a linear extrapolation of risk from atomic bomb survivors using the linear no-threshold assumption/model.
Brenner performed another study in 2002, using the same methodology but with a different exposure. He presented his results using an exposure of 200 mAs for both head and abdominal CT. With these settings the estimated cancer risks decreased linearly as the linear no-threshold assumption would predict. Using the new exposure settings, the estimated lifetime cancer mortality risks attributable to the radiation exposure in a 1-year old are 0.09% for abdominal and 0.03% for head CT. Once again the author has broken down the risk based on the type of scan, sex of the child, and the organ at risk. The estimates are still based on a single CT scan. Both of the papers from this author offer a thorough risk assessment based on the best available evidence that we have regarding the typical CT radiation dose and the cancer mortality data from atomic bomb survivors.

Third article by de Jong et al focused on a specific population that is exposed to CT scans throughout their lifetime. The de Jong et al paper aimed to estimate the excess cancer specific mortality associated with repeated CT scanning of patients with Cystic Fibrosis (CF). Certain centers in Netherlands and Sweden are using CT scans on a biannual basis to measure the progression of disease. The authors used a published CT protocol for CF patients that used settings of 160 mAs and 120 mAs for children younger than 9. They calculated the doses in milliSieverts (mSV) using an impact CT dosimetry calculator and corrected them to pediatric values. Authors assumed that a CT scan delivers a uniform dose to all organs of the body; they applied the estimated dose to a risk model for all solid cancers regardless if they were really exposed by a chest CT scan. They developed seven variations of the model which showed how mortality changes based on changes in median survival and changes in the CT scan interval. They concluded that, when the median survival age was 27.5 years, the cumulative risk of cancer death was between approximately 2% for a relatively low exposure level of 1 mSv. This model
assumed that patients received yearly CT scans from age 2 until death. The critical part of their results section focuses on the fact that when median survival increases to 50 years, as is predicted by 2030, the mortality from both hematologic and solid cancers increased to 13%. This risk decreased to approximately 7% when CT scans are discontinued after the age of 18. The minimum amount of scans per patient in any of the models was 17; this leads to the body being exposed to 16 mSv of radiation. The authors calculated their risks using the radiation doses from the published CT protocol and the radiation risk data from atomic bomb patients such as the Life Span Study of Japanese atomic bomb survivors.\textsuperscript{28} These risk models were developed by the BEIR VII committee.\textsuperscript{22} The lowest cancer risks were seen in the model that used the current median survival and where the CF patients received biannual CT scans. In this case the risks were approximately 1% for both hematologic and solid cancers. Monitoring patients on a biannual basis might be a viable option to monitor progress and the deterioration of individual patient’s lung function if a survival benefit was proven.

Similarly, de Gonzalez et al also estimated the risk of radiation induced cancer (incidence) from chest CT in patients with CF.\textsuperscript{29} They used the same radiation risk models from the BEIR VII committee and the same CT protocol that were used by de Jong et al.\textsuperscript{2,22} One of the differences between the two studies is that de Gonzalez et al used different software, CT-Expo version 1.5, that estimated organ specific radiation doses. The major difference between the two studies is that de Gonzalez et al limited their analysis to organs that are exposed in a regular chest CT exam which further makes their estimates more reasonable and more accurate. Even though they used a different computer program to estimate doses, the effective dose for children was very similar to the de Jong et al calculation and was calculated to be 0.98 mSv and 0.82 mSv for females and males, respectively. Similarly to the study by de Jong et al, CF
patients were also exposed to CT scans on an annual basis starting at age 2. The authors used radiation risk models for sex and organ-specific cancer incidence that were developed by the BEIR VII committee. The committee based their risk models based on the data from the Life Span Study in Japanese Atomic bomb survivors. Background rates of cancer for CF patients, which were assumed to be the same as those in general populations, were estimated based on the Surveillance, Epidemiology, and End Results (SEER) Program cancer registries for 2000-2003. The authors assumed a relatively short lag time of 10 years for solid and 2 years for hematologic cancers. They estimated the total risk of radiation-induced cancer using life table methods as a cumulative lifetime risk and then adjusted for competing causes of death using all cause mortality data from a prospective study of CF patients in France. Assuming a current median age of survival of 36, the estimated radiation risk for all cancer sites was 15.3/100,000 for males (0.02%) and 72.7/100,000 for females (0.07%). These large differences in gender incidence rates are because of the breast cancer risk and a 10-fold increased incidence of thyroid cancer. If the median age increases to 50, as is forecasted by 2030, the incidence will increase to 83.5/100,000 for males (0.08%) and 459.2/100,000 for females (0.46%).

Walter Huda also published a paper that estimated a risk of cancer from chest CT in pediatric CF patients. Using similar methods as others mentioned previously, the total patient risk is related to the effective dose which depends on the dose received by each organ and the radiosensitivity of the organs. The individual effective doses are calculated and then summed together to achieve the total patient effective dose. The author aims to outline a method for estimating radiation doses and from these values he arrives at a corresponding risk. He calculated that an effective dose of 0.55 mSv given to a 5 year old CF patient will lead to a nominal excess risk of cancer on the order of 1.5 per 10,000, with half of these being fatal
These results are an order of magnitude smaller than those initially estimated by Brenner et al. Furthermore, differing from de Jong et al and de Gonzalez et al data, these results are based on a single CT scan and not annual CT scans for the life of the patient. It is also important to note that the dose received from this CF protocol is four times lower than the dose received from a standard pediatric chest CT study. Both the kV and the mAs settings are adjusted for CF patients compared to the conventional chest CT scan for pediatric patients. Therefore, these risks would be much higher in the regular pediatric population undergoing chest CT scan after trauma.

Final paper that aimed to estimate cancer risks from CT exposure was written by Chodick et al. The authors used the same methodology as Brenner et al to estimate the excess lifetime risk for cancer mortality that can be attributed to CT exams in Israeli pediatric patients less than 18 years old. The authors multiplied age, gender, and site-specific lifetime radiation-related cancer mortality risks by the estimated age-dependent doses from CT scans for both head and abdominal CT scans. The authors used the total lifetime risk of cancer based on atomic bomb survivors and the background based on the age and gender-specific mortality rates in Israel. Authors also used the same scan parameters used by Brenner et al which were 462 mAs for head and 404 mAs for abdominal CT. They estimated the age and gender distribution of the frequency of pediatric patients undergoing CT by extrapolating data from the Maccabi Healthcare Services which covers about 26% of children under 18. The authors concluded that based on one year of CT scans, for the entire Israel population younger than 18, there was an excess mortality of 0.29% over the background rate of cancer mortality. The highest excess risk was calculated for patients under the age of 3 who had an excess risk of 0.52%. These results are
very similar, as expected, to Brenner et al who estimated an excess lifetime cancer mortality of 0.35% for patients younger than 15 years.

**DISCUSSION**

There may be a small, but not insignificant, risk of radiation induced cancer from pediatric CT scan. The included studies used a linear no-threshold assumption to base their estimates of radiation induced cancer risk; this model assumes that the response to radiation is linear and that there is no safe level of radiation. The estimates vary from study to study but all show a consistent increase in cancer mortality and incidence. Some of the estimates show that as high as 1 per 1000 CT scanned children will develop cancer. This estimate will most likely pertain to pediatric patients who were scanned 5 or more years ago when the health care community was not aware of the possible cancer risk. CT has been available for approximately three decades and the risk of cancer, as seen in atomic bomb survivors, has been shown to take three or more decades to become apparent. Furthermore, concern regarding CT radiation and the possible link with cancer has only recently been brought up in scientific literature. The increase in scientific dialogue has sparked heated debates from both sides of the spectrum. Therefore, the data that are reviewed in this systematic review are estimates using cancer risk from Japanese atomic bomb survivors and not from actual patients who underwent CT scans.

**ARE THESE STUDIES METHODOLOGICALLY SOUND?**

Perhaps the most important question in this review is whether these studies are methodologically sound and whether the models that are used are appropriate for the current day pediatric radiology practice. With lag time for cancer on the order of several decades, we will only begin to see the possible increase in radiation-related cancer incidence, and subsequent
mortality, in the years to come. The diagnostic radiology community has been using these high exposure settings for 20-30 years and tens of millions of pediatric patients have been exposed at these levels. The damage for children already exposed has been done. Therefore, although the estimates might not be appropriate for children having CT scans at present they are important for those already exposed. Perhaps the Brenner et al and the Chodick et al articles were using appropriate parameters to estimate nearby future incidence of cancer in the cohort of patients who were exposed to higher doses before the policy “as low as reasonable achievable” (ALARA) became a more prominent practice. From personal correspondence with Dr. Lynn Fordham, Chief of Pediatric Radiology of UNC Hospitals, the mAs settings for children are currently set at 30 mAs and 45 mAs for little and big “peds”, respectively. This setting is ten fold lower than that used by Brenner et al and Chodick et al.

Overall, the methodology was very accurate and detailed, and the authors stated that their results can be scaled down linearly based on the different parameters of the CT scan. Even the Brenner’s second paper, which reduces the mortality estimate from his first paper, uses a radiation dose (tube current of 200 mAs) that far exceeds those used by pediatric radiologists. Nevertheless, the possibility that one abdominal CT scan can lead to a cancer in 1 out of 1000 patients should be a concern for the public health community. Both groups of authors used age, gender, and organ-specific estimates of radiation doses and risks to arrive at their estimates. This is important since younger children are more sensitive than adults, females are more sensitive than males, and certain organs are more sensitive than the others.\(^5\) Except the excessive radiation dose that is used to estimate risk, these two papers offer a very good model that can be used to predict radiation risk from any exposure settings. These estimates are not based on extrapolations; rather, they are based directly on the measured excess radiation-related cancer
risk from children who were exposed to the same range of organ doses. Brenner points out, in a response to an editorial, that based on a range of settings from 60-200 mAs and the frequency of CT scans the organ dose to a child is between 5-100 mSV.\textsuperscript{32, 33} This is the dose where a statistically significant radiation-related excess mortality is observed in atomic bomb survivors.\textsuperscript{33} Some children are exposed to multiple scans and data such as this has even greater importance.

The results from Brenner et al and Chodick et al assume that in a particular year each procedure exposed only one child; as has been shown this is not the case. Some children are exposed multiple times in a year and some are exposed only once in their lifetime. Studies have shown that ~30\% of all individuals having a CT will have 3 or more; similarly, multiphase scanning occurs in ~30\% of children which is, in practice, another CT scan.\textsuperscript{8, 20} Estimates put forth by these researchers should be considered when making recommendation regarding repeated exposure or multi-phase scans. Therefore, the use of these data would be useful in cases where children are repeatedly exposed such as in scanning for chronic conditions like Crohn’s disease, Ulcerative Colitis, and Cystic Fibrosis where CTs are used for exacerbations or for determining progression of disease.

de Jong et al also used CT scan exposure settings (160 mAs and 120 mAs if less than 9 years old) which are higher than current practice. Furthermore their results were not based on the sensitivities of different organs and were rather based on a uniform dose distributed homogenously throughout the body. Research has shown that different organs have different radiosensitivities. The thymus, lung, and breast are particularly sensitive and are directly exposed by a chest CT scan.\textsuperscript{34} If they had performed an analysis based on only these three organs their risk estimates would have been significantly lower. Furthermore, de Jong and al provide the least amount of information regarding their calculations and therefore their surprisingly high
estimated risks should be questioned. The methodology used by de Jong et al is poor and therefore their conclusion and their high estimates should be critically scrutinized and viewed with caution.

Results by de Gonzalez et al provide a methodologically sound analysis of the estimate of radiation-induced cancer risk from pediatric CT scans. The authors used a CT protocol for CF patients which emitted low doses of radiation that was estimated to be 0.98 mSv and 0.82 mSv for females and males, respectively. More importantly, unlike de Jong et al who assumed that the radiation dose is delivered uniformly to the whole body, the authors used organ-specific radiation doses and risk models. The authors used relatively short lag times for both leukemia (2 years) and solid cancers (10 years) and this would have potentially overestimated their results. They assumed that children were exposed on an annual basis to a low dose CT scan. Once again, these authors assumed the linear no-threshold assumption which has been embraced by the scientific community.

Finally, Huda performed a very thorough analysis and used methodology very similar to de Gonzalez et al to estimate radiation-induced carcinogenesis. He used very precise, weighted factors, for specific organ radiosensitivities to estimate radiation-related risks; he summed the doses to each organ and arrived at an overall effective dose. In addition, the CT protocol used exposed patients to 20 mAs which lead to an effective dose of 0.55 mSv—relatively low for CT standards. Huda estimated the incidence, and the consequent mortality, based on a single CT scan but his results can be easily modified for repeated scans as was done by de Gonzalez et al. The effective dose is almost half compared to those used by de Gonzalez et al and most closely represents doses used today in pediatric radiology practice. Huda’s analysis is the most balanced one considering the detail of the estimate and the great underlying methodology.
WHAT OTHER DATA IS THERE TO SUPPORT THE LINK BETWEEN MEDICAL RADIATION AND CANCER?

There is much controversy among researchers in this field whether radiation leads to an increase in cancer. The controversy is supported by data on both sides. Data from radiation treatment of benign disease shows that radiation may lead to cancer. Pediatric patients have been irradiated in the past for such conditions as *tinea capitis*, enlarged thymus, and scoliosis. A pooled analysis of seven studies was performed which included children who received radiation for enlarged thymus, *tinea capitis*, various head and neck conditions (enlarged tonsils in particular), childhood cancers, and atomic bomb survivors. In this study the authors showed that a mean dose of 0.1 Gy leads to a significantly increased relative risk; the excess relative risk per unit Gray was 7.7. The pooled analysis showed a clear linear dose response relationship for patients who were exposed before the age of 15.

Patients with scoliosis have a large number of x-rays as children and young adults and therefore would be another population that could be studied to assess the radiation related cancer risk. Furthermore, most scoliosis patients are female and the radiation exposes the breast which is a radiosensitive tissue. Doody et al performed a retrospective cohort study to evaluate the pattern of breast cancer mortality, particularly to evaluate the risk associated with diagnostic radiology. In this cohort the average number of examinations was 24.7, which leads to a mean estimated cumulative dose to the breast of 10.8 Gy. The standardized mortality rate in the scoliosis cohort, as compared to the breast cancer rates in the general population, was 1.69 (95% CI=1.3-2.1). The authors also stated that the risk increased with the increasing number of radiology examinations. This study suggests that at even low protracted doses there is a risk of breast cancer. This increase in risk is more than likely linked to the fact that the exposure took
place at a time when the breast is particularly sensitive to the radiation. The authors state that most of the examinations performed in this study were done before 1976 when the doses were approximately 20 times higher than with current techniques.  

Thymus irradiation data also shows an increased risk of cancer. The authors studied the incidence of breast cancer in a cohort of 1201 women who received x-ray treatment in infancy for an enlarged thymus. The authors showed that, as compared with their sisters, the irradiated cohort had increased risk of cancer (rate ratio 3.6). The mean estimated dose to the breast in this study was 0.69 Gy. Similarly, studies have shown that infants irradiated for skin hemangiomas have an increased risk of cancer.  

In this study the mean absorbed does to the breast was 1.5 Gy. Both of these studies show that even low doses can lead to the development of cancer in susceptible young patients. Therefore, these data from tinea capitis, thymus irradiated patients, and from scoliosis patients can be used to support the hypothesis that CT scanning could lead to an increased cancer rate. There is much controversy whether CT scans can lead to cancer. Data such as this support the possibility of a relationship between CT and cancer.

CAN WE USE THE RADIATION RISKS FROM ATOMIC BOMB SURVIVORS TO ESTIMATE CANCER RISK IN OTHER PEDIATRIC PATIENTS?

Another important question that needs to be answered when thinking about these estimates is whether they can be generalized to the US and to other populations around the world. Are the background characteristics, most importantly cancer rates, of the Japanese atomic bomb cohort the same as those of the USA and other countries around the world? Furthermore, were the victims of the atomic bombs more susceptible to the effects of radiation?
Radioloeidemiological studies are confounded by factors such as environment, life-style risk, and diet.\textsuperscript{21} These may act as tumor initiators or as tumor blockers.

Infrastructure in Japan was devastated by the bombings that destroyed sixty-six cities, including the droppings of the two atomic bombs on Hiroshima and Nagasaki. After the war “\textit{kyodatsu} conditions” of exhaustion and despair overwhelmed many Japanese. John W. Dower displays the post-war situation clearly when he says “the streets of every major city quickly became peopled with demoralized ex-soldiers, war widows, orphans, the homeless and unemployed—most of them preoccupied with simply staving off hunger.”\textsuperscript{39} By 1945, factory absenteeism rose nationwide as individuals took time off to bargain and barter for food in the countryside. Emergency diets were instituted that consisted, among other things, of sawdust, silkworm cocoons, worms, grasshoppers, mice, and rats. Elementary school children were, on average, shorter in 1946 than their counterparts in 1937. At its worst, during mid-1946 and mid-1947, the government estimated that rations supplied only one-quarter to one-third of the required 2,200 calories.\textsuperscript{39}

With the state of food shortage in the country as the background, these malnourished individuals would have been more sensitive to the radiation exposure from atomic bombs and their natural immune responses would not have been able to protect the body from the radiation induced damage.\textsuperscript{40} As mentioned in the introduction of this paper, radiation leads to formation of hydroxyl radicals that lead to double stranded DNA breakage. Antioxidants, which are plentiful in fruits and vegetables, are known to act as a buffer that eliminates radicals and other signs of oxidative stress. It is reasonable to argue that patients getting exposed to CT scans, in the 21\textsuperscript{st} century, have the necessary antioxidants which eliminate the radicals that are formed from the harmful radiation. The effects of nuclear radiation would have been significantly more
deleterious than they would have been in appropriately nourished patients and therefore the estimates would have to be scaled back in CT scanned patients.\textsuperscript{40}

Atomic bomb survivors have been followed in the Life Span Study which included a cohort of 86,752 people who were within 10 km of the epicenter. Individual dose estimates are available for 85\% of this cohort.\textsuperscript{41} Nevertheless, because the location and the shielding of the individuals can not be accurately ascertained, there is a great deal of imprecision in the individual dose estimation. The problem in the process of dose estimation is whether the person was in direct line of the radiation or was the person shielded by a building or a set of buildings; furthermore, being on the distal side of the building would shield the individual from the radiation. Furthermore, location ascertainment was placed into two broad groups less than 3 km and 3-10 km from the epicenter. The data showed that the excess solid cancer risk appears to be linear even in the 0-120 mSv range.\textsuperscript{41} In addition, all of these estimates might have overestimated the real risk because newer therapies have been developed to improve survival since the collection of atomic bomb data.\textsuperscript{2} Furthermore, the survivors of atomic bombs were exposed to a fairly uniform dose of radiation throughout the body while CT delivers a localized radiation exposure.\textsuperscript{1} The estimates that were put forth by all the groups would have to be adjusted if these issues were taken into consideration. There is a great deal of uncertainty in the cancer risk estimates as put forth by the Japanese atomic bomb survivors. Therefore, their use in estimating CT associated cancer risk should be viewed with caution.

In terms of the Cystic Fibrosis patient’s risk, one would also have to question whether these estimates can be used to predict excess mortality rates over the background rate. Estimates should be based on background cancer rates of children similar to the ones who are being scanned; therefore, the authors should have used the cancer rates in CF patients as the
background rate. This is not feasible option as these patients usually do not live long enough to develop cancer. All the papers assume that cancer rates in CF patients are the same as in rest of the population and there is evidence to support this assumption.\textsuperscript{42} This assumption is based on the fact that CF patients are exposed to the same level of cancer risk factors as the general population. Nevertheless, CF patients have lower rates of smoking and therefore they would be predicted to have lower rates of lung cancer.\textsuperscript{43} In this case the cancer risk estimates might have overestimated the real cancer risk because of the lower background risk from cancer. On the other hand, due to chronic lung inflammation that CF patients are exposed to, the estimates could be grossly underestimated. Finally, doses were calculated based on average size of pediatric patients. Cystic Fibrosis patients are often malnourished, although treatment has focused on maintaining proper nutrition, and hence weigh significantly less than their peers. Therefore, their thinner bodies would be exposed to a larger penetrating dose to each organ.

As the survival for CF patients continues to increase, the prospect of lung cancer may become a real problem. The scientific community will have to figure out if this hypothesized increase in lung cancer is from radiation or from chronic inflammation. Furthermore, there are no studies that show a survival benefit of CT scanning in CF patients.\textsuperscript{2} Only when the benefits of CT scanning have been shown to increase survival or change the management of disease should CT scanning become standard practice in pediatric hospitals that treat CF patients.

**DOES THE LINEAR NO-THRESHOLD ASSUMPTION APPLY?**

The papers appraised in this review all assumed that the linear no-threshold assumption holds true for low-dose radiation. This is an assumption that three of the leading scientific authorities have made.\textsuperscript{22, 44, 45} The current knowledge that we possess about the field supports the assumptions that the cancer risk from low dose radiation decreases linearly with a decreasing
dose. Brenner et al summarized the popular position perfectly by concluding that “given that it is supported by experimentally grounded, quantifiable, biophysical arguments, a linear extrapolation of cancer risk from intermediate to very low doses currently appears to be the most appropriate methodology.”

There are four other dose response relations for estimating the risk for doses below 5 mSv, a dose that would correspond to a pediatric patient becoming exposed to one CT scan in their lifetime. This is the dose at which we can not use epidemiological data alone to calculate estimates.

One scenario is represented by a downwardly curving dose-response relationship such as portrayed in curve b in Figure 3. In this scenario patients are more sensitive to low dose radiation and therefore the linear no-threshold assumption would have underestimated the true
risks. This might be the case in subpopulations of people who are hypersensitive to radiation.\textsuperscript{47} Specific radiosensitive subpopulations have been identified such as the \textit{Atm} and \textit{Brca1} heterozygotes.\textsuperscript{46} Another interpretation of the downwardly curving dose-response relationship is the bystander effect. The bystander effect occurs when radiation-damaged cells send out signals to adjacent cells which can potentially lead to oncogenic damage to these bystander cells. The bystander effect is characterized by steep response particularly at low doses. At higher doses the bystander effect is not seen because the bystander cells have already been saturated.\textsuperscript{46} There is evidence for this effect in laboratory studies but the effect on low dose x- or γ-ray has yet to be established.\textsuperscript{48}

On the other hand, there are two scenarios where the linear no-threshold assumption would have overestimated the true cancer risk. One occurs where there is a threshold that needs to be reached to lead to the induction of cancer (curve d, Figure 3). One example is radiation-induced sarcoma which is seen after radiotherapy in high dose regions but not at distant organs which are exposed to low doses.\textsuperscript{49} A study of a sub-cohort of the Japanese Life Span Study showed that there is an increased risk of cancer for a radiation dose in the range of 0-0.1 mSv.\textsuperscript{50} Clearly, there is data to support both a threshold model and a no-threshold model for radiation risk. As mentioned earlier, three of the leading authorities on radiological protection have assumed that there is no threshold for radiation to cause harm to the human body. This might be the safest assumption considering that there is no data to show that low doses are not harmful. Another scenario occurs when there is an upwardly curving dose-effect relationship (curve c, Figure 3).\textsuperscript{46} This is seen in acute exposures that lead to leukemia and chromosome aberration induction. Nevertheless, the upwardly sloping response relationship is seen only in high dose cases.\textsuperscript{46}
Final scenario occurs if the radiation reduces the background incidence of some other events that would have contributed to mortality.\textsuperscript{46} This is called the hormetic response (curve e, figure 3). Some experiments have shown that low dose radiations can increase longevity in animal models.\textsuperscript{51} It is important to note that the increase in longevity is more likely to be associated with a radiation-induced enhancement in the immune system rather than a beneficial stimulation of DNA repair mechanisms.\textsuperscript{46} The data is weak, inconsistent with large uncertainties, and there is a lack of consensus on how hormesis should be defined.\textsuperscript{21} Compared to this model the linear no-threshold assumption would have led to an overestimation of the true risk.

MINIMIZE UNNECESSARY CT SCANS—THE RESPONSIBILITY OF ALL HEALTH CARE PROFFESIONAL CARING FOR PEDIATRIC PATIENTS

The best solution to the steadily increasing CT use in pediatric patients and the associated increased risk of cancer would be to stop performing CT scans. Clearly, there are many cases where the CT scan is indicated, is the most appropriate tests, and in those individuals the benefits far outweigh the small individual risk. Pediatric health care professionals should be more judicious when ordering CT scans and the radiologist and the technician should inspect all CT requests that come in. A poll of the participants at a radiology conference found that they considered about a third of the pediatric CT scans to be unnecessary.\textsuperscript{52} We are taught in medical school the importance of physical exam and history of present illness. Unfortunately, once we get out of medical school and into the clinic we do not rely on those skills and opt to use technology to supplement our clinical knowledge about the case. As mentioned earlier, it is hard to define how much of this overuse is due to the practice of defensive medicine and this question should be researched further. This is even more important considering that physicians are not
aware of the inherent risk of cancer and of the radiation dose that is emitted during the procedure. A more recent study surveyed by the American Pediatric Surgical Association found that only 55% of the surgeons believed that there was an increased risk of cancer. Furthermore, 75% of the surgeons underestimated the radiation dose as compared to the x-ray. The authors stated that pediatric surgeons were more aware of the risk and the doses as compared to other physicians as seen in previous studies. The authors again make the point that education of pediatric health care professionals will be very important in minimizing the radiation induced cancer risk. Surgeons talk in great detail about the risks and benefits of surgery but they do not have the same conversation about the risks and benefits of CT. Perhaps, the solution is in the introduction of informed consent forms for the administration of CT scans.

Many, including pediatric radiologists, have written about the need to replace CT scans with ultrasound or MRI. Ultrasound uses high frequency sound waves to develop images of the body. There is no know cancer risk from ultrasound and it is a relatively inexpensive technology. MRI on the other hand uses powerful magnetic fields to produce images inside the body. MRI is significantly more expensive than CT and this has limited its use in replacing CT as the test of choice. In the future as the technology becomes cheaper the use of MRI will more than likely increase. Another reason for limited use of MRI in pediatric radiology is the fact that image capture can take as long as 30-45 minutes, a prohibitively long amount of time for a pediatric patient to lay motionless. A significant drawback to performing MRI on young children is that they often have to be sedated with anesthesia which in itself has possible side effects. Pediatric clinicians and the pediatric surgeons have to do everything in their power to minimize unnecessary scans; then it is up to the pediatric radiologist and the technician to follow
the “as low as reasonably achievable” (ALARA) concept and minimize the radiation dose that children are exposed to.

IF THE EXAM IS ABSOLUTELY NECESSARY HOW DO WE MINIMIZE THE DOSE OF RADIATION: PLAYING WITH THE SETTIMGNS

One of the easier ways to decrease the doses that children are exposed to is by changing the tube current and tube voltage settings for studies. Due to the recent knowledge and dialogue about the damage of radiation, especially in young children, there has been a push by the radiologists, radiologic technologists, and CT manufacturers to make it harder to expose children to excessive doses. Part of the problem lies in the fact that an increase in radiation dose does not lead to a reduction in image quality as it does in conventional radiography. In conventional radiography an overexposed image will lead to a dark examination.\textsuperscript{19} In contrast, in CT exams, the higher the patient dose the more aesthetically pleasing the image.\textsuperscript{55} In pediatric radiology some noise is acceptable and does not take away from the diagnosis. Previous studies have shown that a dose reduction of 50-75\% may be possible without compromising diagnostic quality.\textsuperscript{54}

Image quality in CT is determined by both spatial resolution and contrast. The tube current (milliAmperes) affects spatial resolution and the tube energy (kiloVoltage) affects both spatial resolution and contrast.\textsuperscript{55} These two parameters have become the focus when trying to decrease the dose that children are exposed to during a CT exam. An increase in both of these parameters leads to a decrease in image noise and conversely, a decrease leads to an increase in image noise.

An easy way to reduce the radiation dose is to adjust the settings on the CT with the tube current being the most likely target. The tube current, which is the number of photons generated
by the x-ray tube, is multiplied by the gantry rotation time to yield the unit of mAs. A reduction of 50% in the tube current (mAs) leads to a 50% reduction in the dose. This in turn leads to a 50% reduction in cancer risk as was explained in this review by the linear no-threshold model. These lower current settings are recommended for small children and for chest scanning where, in both cases, there is less solid tissue that the radiation has to penetrate. The one drawback is the fact that images made with less tube current will have more mottle (signal noise) which might make evaluation more difficult. We have to be careful of not decreasing the dose to a level where evaluation will be impossible; this will lead to an incomplete clinical picture and the child might have to be screened again. Newer CT scanners are equipped with automatic tube current modulation which leads to the tube current being adjusted during the exam based on the first pass-through scout film of the child. Similarly, decreasing the gantry time from 1 second to 0.5 second would halve the tube current dose and therefore the radiation dose for the child. This reduction also decreases the time in the gantry which can be traumatizing for children and takes away the need for sedation and the associated risk. Finally faster capture of images with a decreased gantry time leads to less motion artifact.

Another area of change would focus on changing the tube voltage or the energy of the x-ray. A reduction in kV from 120-140 kV can lead to a decrease in radiation dose although that depends on each individual CT machine and on the specific manufacturer protocols. On average, with the tube current staying the same, a tube potential of 100 kVp resulted in effective doses that were 105% higher than those at 80 kVp and 210% higher than those at 120 kVp. Pitch, which is determined by beam collimation and table speed, can also be altered to decrease the dose. A higher pitch will lead to a decreased radiation dose. But as seen in the other parameters
it comes at a price. It leads to helical artifacts, degradation of section-sensitivity, and decrease in spatial resolution.\textsuperscript{57}

Multi-phase scanning has also increased so that in 2001 one third of pediatric CT is performed using multiple phases.\textsuperscript{20} Each additional phase is another CT exam that has a cumulative affect on the radiation exposure. The practice of multiphase scanning is rarely performed in pediatric tertiary care hospitals. Paterson and Frush suggest that this is still the case outside of children’s specialty hospitals.\textsuperscript{55} They further suggest that only 1-3\% of body examinations in pediatric patients need to be multiphase examinations. There is no clinical data to support the notion that routine multiphase examination improves diagnostic capabilities.\textsuperscript{58}

The number of repeat examinations has also led to a drastic increase in pediatric CT use. Research has shown that 30\% of the patients undergoing CT have at least 3 scans, 7\% have at least 5, and 4\% have at least 9.\textsuperscript{8} Part of this can be explained by the lack of communication between hospitals that leads to repeat examinations just because the images were not transferred to the accepting hospital. Furthermore, there is a significant amount of repeat imaging that happens to follow-up progression or resolution of disease. For such examinations it might be acceptable to perform a lower radiation scan and to limit the region of exposure.\textsuperscript{55}

Finally, radiologists and technicians should make sure that the abdominal scan is limited to the abdomen and therefore does not expose the radiation sensitive gonads. Similarly, examination of the aortic root does not need to extend to the lung bases or up to the thyroid.\textsuperscript{55} Equally as important, repeat images for follow-up should not only be performed with lower doses but should also have a very precise and limited scan range. It is the responsibility of both the radiologist and the technologist to make sure that these things are being done on repeat exams.
EDUCATING THE HEALTH CARE PROFESSIONALS: PEDIATRICIANS, NURSE PRACTITIONERS, FAMILY MEDICINE DOCTORS, (ADULT) RADIOLOGISTS, PEDIATRIC SURGEONS AND GENERAL SURGEONS

As is the case often in public health the best way to make changes is to get to the root of the problem. We are taught in medical school about the value of preventative care and its ability to prevent chronic disease. Herein, I propose something a bit different but same in principle. We have to educate future health care practitioners before inappropriate habits are formed and ingrained. As has been noted elsewhere in this paper, the diagnostic certainty of CT forms a positive feedback loop for the health care professional, the patient, and his or her family. Pediatric health care professionals are rarely taught, through their medical school years or through residency, about the harms of CT use. Part of the reason for this has been the fact that this issue has only surfaced in recent years. At two local, well known, academic hospitals there is no program in place to teach medical students or residents (pediatric, surgery, or family medicine) about the harms of radiation especially in the pediatric population. It is critical that residency directors focus more on this issue in the coming years. In my personal experience I noticed that surgery interns and residents were ordering CT exams on pediatric patients without consulting the attending physicians. I understand that the amount of work in big tertiary care setting prevents more communication between residents and attending physicians regarding the ordering of tests but that should not be used as an excuse. Unfortunately, these residents have never been taught about the risks of cancer from CT use. Nevertheless, the benefits of appropriate CT tests far outweigh the potential risk to the individual.

Residents receive didactic lectures more or less every day. A single lecture about the harms of CT and the associated radiation will teach residents and medical students about the
increased risk of cancer. Similarly, a lecture in this type of setting should focus on developing open lines of communication with pediatric radiologist regarding the appropriateness of a certain tests. Grand rounds for house staff also offer great venue for the dissemination of such information. The earlier that we educate health care professionals about the harms of CT scanning the more of an influence we will have on their decision making in their practice.

Another important group that we need to educate is the patient and his/her family. There has been a lot of inflammatory public outcry about CT use ever since the initial Brenner et al paper was published. The health care community has to better digest this information and teach the public about the low, although not insignificant, risk of cancer. The patient’s family, properly educated, can serve as the patient’s best advocate. When receiving their exam the family should ask whether the CT scan is appropriately sized for pediatric patients. Pediatric radiology practices have specific accreditation via the American College of Radiology that certify them to perform CT exams. If community practices are constantly questioned regarding their use of pediatric technique they will change their protocols if they see that they are losing business to practices that are accredited. If the public demands that things need to change, regulators will follow suit; manufactures will follow as well when they are mandated by law.

Manufactures are usually the last to change as such adjustments often presses them to invest more money in a different technology. More recently, manufactures have developed automatic tube current modulation where the tube current is adjusted during a CT scan based on regional need for more or less radiation. This change in tube current is based on scout film that scans the patient. It would be inappropriate to scan the upper chest with the same tube current as the lower part of the chest. The upper chest includes the lungs which consist mostly of air; the lower part of the chest includes the heart and therefore more tube current is needed to penetrate the
tissues. This technology is expensive but major specialty children’s hospitals in the country have a CT scanner that is capable of automatic tube current modulation (Frush DP, personal communication).

In my conversation with Dr. Donald Frush (Duke Chief of Pediatric Radiology) he mentioned that every test is appropriate but that there is a different degree of appropriateness. Sometimes CT scans are always appropriate and sometimes their appropriateness is questionable. In this later instance patients can either be followed clinically or can be scanned with either ultrasound or MRI. There have been no studies that looked at the unnecessary use of CT scans because this is a contentious issue. What constitutes unnecessary is going to mean something different to every single health care professional. Every test that we do in medicine should be performed for a specific reason; the results of that test should affect the clinical management of the patient. It is not appropriate to order a CT scan if we do not know how this will change the way we treat the patient. Unfortunately, due to the wider availability and ease of use of CT, this has been the case. As I have mentioned earlier in this paper pediatric radiologists stand as the last line of defense to prevent children from being needlessly exposed to radiation. Every pediatric radiologist that I have spoken with wishes that they fielded more phone calls about the appropriateness of tests especially if the ordering physician was not sure whether the test was indicated. This creates open lines of communication, teaches the ordering physicians about appropriate test for specific clinical questions, and most importantly saves children from the long term harms of radiation.

The dialogue that this issue has caused in scientific circles can only benefit the patients who are at risk. There has been tremendous improvement in the appropriate use of settings for pediatric patients undergoing CT. Much has already been done through the hard work of
pediatric radiologists around the country. They have advocated for lower CT settings, for the use of judicious CT scans, and for the replacement of CT by ultrasound or MRI in appropriate settings. Nevertheless, more work needs to be done to educate adult radiologists who practice and read pediatric radiology imaging in community hospitals. This is where future advocating work has to focus on because tertiary care centers with children’s hospitals are way ahead of the curve (Frush, DP and Fordham L, personal communication). These radiologists should have continuing medical education (CME) classes that should focus on the risk of cancer from CT scanning in pediatric and in young adult patients. These classes should also focus on the strategies that can be used by the radiologists to minimize the risk to pediatric patients. Just as important is the fact that the ultimate CT settings are the responsibility of the technologists. Therefore it is imperative that the technologists are involved in this discussion. This begins with their respective education and continues with their voice being included in the proper adjustment of settings for pediatric patients.

More recently the Alliance for Safety in Pediatric Imaging has formed the Image Gently campaign that has set out to protect the feeblest members of our society. The Alliance was established in July of 2007 and the website was rolled out on January 22, 2008. The aim of the campaign is to “change practices by increasing awareness of the opportunities to lower radiation dose in the imaging of children” (www.imagegently.org). The picture on the main page is of a little girl with an adult size life vest and a quote “One size does not fit all”. This analogy shows that it is inappropriate to scan a little child using the same settings that a grown adult is exposed to. The Alliance is composed of over 400,000 health care professionals who aim to promote appropriate and high quality CT scans for pediatric patients. The first phase of the plan is aimed at radiologists who practice mostly adult radiology but also perform on some pediatric patients.
The Image Gently campaign advocates child size kV and mAs settings, only one pass through the scanner (one phase), and scanning of only the indicated area. They also advocate scanning only when necessary. It is too early to evaluate the effect that this program has had on pediatric CT scanning practice but it is exactly the intervention needed to reduce the potential risk of cancer in pediatric patients.

There has been success in getting this information to the practicing pediatric radiologists in the community and there is no reason to believe that the Image Gently campaign will not have similar success in targeting adult radiologists. In a study that is currently in press the authors found that there has been a significant decrease in kV and mAs which directly affects the level of radiation. The authors compared their results to a previous study that looked at this same issue based on a survey performed in 2001. Both groups surveyed members of the Society of Pediatric Radiology (SPR). The mean mAs setting used for all age groups in pediatric patients decreased between 31 and 61 mAs (p<0.001). The most significant decrease was seen in children 0-4 years of age; the percentage of respondents using 100 mAs or less increased from 42% to 97% for routine chest CT and from 28% to 88% for routine abdominal CT. The authors concluded that this change was most likely due to the increased awareness about the harms of radiation. These changes are a product of SPR’s ALARA conferences, multiple journal articles about the risk, practice guidelines from the ACR and CT accreditation programs, and as a result of manufacturer’s protocols for pediatric patients. One limitation of this study is the fact that it surveyed pediatric radiologists and therefore is not able to make any conclusions regarding non-SPR members. Also most of the respondents were from university and pediatric hospitals so these findings might not adequately represent pediatric practice in the community settings where
there are no SPR members. Further research is needed to clarify the changes in the community settings where adult radiologists perform pediatric CT scans.

SHOULD WE USE INFORMED CONSENT FORMS WHEN GIVING PATIENTS CT SCANS

The use of informed consent is prevalent in all parts of the hospital and especially when doing minor procedures and surgeries. Any procedure that is performed in the hospital or in the clinic office comes with an informed consent form. The doctor discusses what is involved in the procedure, the benefits and the potential harms of the procedure, and the possible alternatives. The use of informed consent has not yet made it to the field of radiology (except in cases of interventional radiology). Unfortunately, we as health care professionals are not completely informed. Experts continue to debate whether the low doses emitted by CT scans can really lead to cancer. Furthermore, will there be different informed consent forms for different people. Will a 15 year-old child who has already received 10 CT scans be given the same informed consent form as a child who has received no previous scans? Perhaps the biggest concern is that it will make the risk of approval even more troublesome for the parents. CT is clearly indicated in many circumstances and prolonging the time to scan can have deleterious consequences for the child. Also there is no standard of care that is practiced in the whole country. There are centers that use ultrasound and MRI more than CT especially in pediatric patients (Frush DP, personal correspondence). Most of the law suits that occur in the field of medicine are due to the lack of communication between patients and doctors. Talking to patients and their parents about the possible risks of cancer in the future may be appropriate especially if more research in the future shows that the risk is directly associated with CT scans. Currently, the best method is to educate the patient, if they are interested, about the possible risk and harms of CT use.
WILL WE EVER KNOW THE TRUE RISK? MORE DATA ABOUT THE DIRECT LINK, IF ANY

Much of the information that we have about the harmful effects of low dose radiation comes from the atomic bombs survivors in Japan. The data from these cohorts are used to predict radiation related risks from CT scans. In order to effectively evaluate radiation related risks, investigators would have to conduct a large epidemiological study of hundreds of thousands of people and follow these people for three to four decades. It is hypothesized that this long lead time is needed for radiation induced cancers to be expressed.

To perform a study to detect an increase from 0.2000 (which is the 1 in 5 risk in the general population for all cancers) to a 0.2002 (which includes the general population risk plus the additional estimated 1/5000 risk from CT scans) one would need hundreds of thousands if not millions of exposed individuals. It is important to note that some estimates place this number as high as 1 per 1000 CT scans so perhaps a smaller number would be needed. The large number of individuals needed for such a study is precisely why many of the studies have predicted the incidence of cancer from radiation by comparing their data with those of the Japanese atomic bomb cohort. I propose such a large scale study that will follow children exposed to CT scans until the development of either hematologic or solid cancer. This type of study will require up to millions of subjects.

Therefore, the best study design for a study such as this would be a prospective cohort study. This is the same design as was used by the Japanese and American researches studying the effects of the atomic bombs. The exposed would be children (0-18 years of age) that were exposed to one or more CT scans in their lifetime, while the unexposed would be children who did not have any CT radiation exposure. It is possible that some of the unexposed would become
exposed throughout their lifetime and therefore they would be moved to the exposed group if they were scanned before 18 years of age. The exposed children would be the population at risk for establishing CT related cancer. This sort of study would be suitable in a country where there is a centralized system of medical records such as Canada and UK. Also, in this type of setting you could assume that there was equal access to health care both by the exposed and the unexposed children. Therefore, one group would not be more likely to receive care and therefore be more likely to have a cancer detected; this would avoid the possibility of detection bias. This study could also be performed in the United States and would probably have to be done using either a HMO cohort or the Medicaid cohort since these provide for large registries that may facilitate easier exposure identification. In this instance the unexposed children would be taken from those same HMO and Medicaid registries. The study will have to control for all the other factors that cause cancer. I believe that this will be a feasible undertaking considering the size of the study.

The exposure measurement would have to be accurate for this trial; my worry is about recall bias if people, especially young kids, would have to remember if they had a CT scan. Many patients are not aware of the events they went through in the hospital. Furthermore, young children do not remember their hospital stays or the procedures that were performed. Finally, many patients, who were repeatedly exposed to CT, are not sure how many times they were exposed or whether there were multiple phases performed in the study; this data is equally as important since repeated CT scans are cumulative and lead to a cumulative increase in risk. Therefore, countries that have universal health care would be the most appropriate sites to study the cancer risk since the measurement of exposure could be easily obtained and would be a reliable measure. The unexposed children would also be ascertained from the same national
registries and would not have been exposed to CT scans. Prospective cohort design would be more efficient and cost effective than a retrospective design. A retrospective design would include all people who were not necessarily exposed to a CT scan as children. Then the research team would have to look back through the records to find whether those individuals were exposed to a CT scan in their childhood. Recall bias would be the biggest reason that I would not undertake a retrospective cohort studies since the measurement of exposure is so important in this study.

The outcome of interest for this cohort would be the incidence of cancer either hematologic or solid. The incidence of cancer between the unexposed and the exposed children could be compared to ascertain whether CT scan and the associated radiation do have an effect on the incidence of cancer. For such a sort of design and study focus we will need to take care about the induction and latent period which will be significant as mentioned in the introduction. Furthermore, since this study will take several decades, due to the long induction and latent period, tracing of subjects will become an issue. Finally, the study is based on the linear no-threshold assumption, which has been validated by several committees, that states that any amount of radiation can be harmful to the body.\textsuperscript{22, 44, 45} It is possible that small levels of radiation could have more of an impact or less of an impact based on the individual and that this relationship might not be linear.\textsuperscript{46} Drop out of exposed patients will be a limitation of this study but study researchers should contact study participants to maintain current information. Also, the fact that this study will take place in a universal health care setting will make the ascertainment of cancer incidence a much less difficult task. There should not be as many patients lost to follow-up as there are in other cohort studies.
Several data points will be collected in this study. The outcome of interest will be the incidence of cancer and will be measured in person-years. From these values we can calculate the risk ratio for the development of cancer in the exposed group as compared with the unexposed group. An additional data focus of this study will be to attempt to calculate the effective dose received by the patient from each CT scan. In the current estimates of cancer risk from CT scans the doses that are used are only estimates. A total effective dose should be calculated for each patient and can be cumulatively added for each additional CT scan performed on that patient. Calculation of an effective dose takes into account the location of the radiation and the different radiosensitivities of organs.\textsuperscript{62} The purpose of calculating an effective dose is to compare the radiation exposure of the brain to that of the chest; this measurement reflects an equivalent whole body dose that can be used to predict a stochastic risk. Calculation of an effective dose is a challenging undertaking especially with the automatic tube modulation which changes the mAs settings during the exam. There are many methods for measuring the effective dose from a CT exam such as the Monte Carlo method that uses a mathematical patient model.\textsuperscript{62} Unfortunately, determining the radiation dose to each organ is problematic and a direct measurement of the dose from a CT scan is not feasible. Furthermore, estimating the effective dose for each patient is made more difficult by the fact that each patient has a different weight, height, age, sex, gender, and body composition.\textsuperscript{62} Hopefully, future research will be able to estimate patient specific radiation dose and not use estimates based on mathematic patients.\textsuperscript{62}

The limitations of this study will be the fact that loss to follow up will be a major problem. The point of doing this study in universal health care system would be to minimize this loss. Furthermore, this study will be expensive since it will take place over several decades and will enroll hundreds of thousands if not millions of patients. Finally, it will be time consuming
and it will take a group of researchers who are particularly involved and invested in the care of pediatric patients to carry out the research and the subsequent analysis.

The criteria used to form a conclusion will be based on the difference in incidence rates between the exposed and the unexposed groups. The study will also calculate a risk ratio. Clearly if the study results show that there is a 1 in 1000 chance of radiation related cancer in pediatric patients scanned with CT we will have a tremendous public health problem based on the amount of pediatric CT scanning. We rank as the highest per capita spender in health care in the world and some of the most expensive areas are those of imaging. Other countries have been able to limit the amount of imaging while not decreasing the quality of care. United States on the other hand does not use the technology available to the best possible extent. Even if the null hypothesis is not rejected we are scanning too many children unnecessarily either due to the practice of defensive medicine, lack of communication between institutions, or due to the lack of knowledge about the proper use of technology. We could save the US government and the employer based health care system billions of dollars by using imaging more appropriately.

This study could have tremendous public health implications based on the data that it provides. Applying very small risks to over 4 million children that are exposed each year can create a public health concern for all health care professionals that are involved in the care of this population. If the data showed that there was a risk between 1 per 1000 scanned and 1 per 5000 scanned than this data should be seriously considered when making clinical decisions. If this prospective cohort study proves that CT scans do lead to an increase in cancer this will lead to specific recommendations that will have a significant public health impact. There is wide agreement by all the involved parties that the benefits of an indicated CT scan far outweigh the potential harm. The key word in this last sentence is “indicated”. It is hard to estimate how
many scans are not indicated and are considered repeat scans, unnecessary scans, or CT scans that could have been replaced by ultrasound or MRI. The practice of defensive medicine also increases the number of non-indicated scans although, once again, that number is hard to quantify.\textsuperscript{12, 13} If this study proves a relationship between CT scans and cancer it will have the greatest affect on the amount on unnecessary scans. The indicated scans will continue to be performed as CT scans are truly a great diagnostic tool if used in appropriate ways.

One of the main barriers to more appropriate CT use is the lack of physician knowledge (ER, pediatricians, surgeons, and radiologists) about the radiation dose that a typical CT scan emits.\textsuperscript{26} Perhaps a study such as this will lead to better education of pediatricians, surgeons, and nurse practitioners about the proper use of imagining technology and about the associated cancer related risks. On the other hand, we do not have to wait for these results to make changes in the way we use imaging. The health care community should focus on decreasing the use of imagining considering that we know that there are levels of radiation that have been proven to be harmful to the human body. The people that can help most in this endeavor are pediatric radiologists. They are specifically trained in what tests should be used to answer specific clinical questions and are also trained in the CT settings that can minimize radiation doses.

\textbf{LIMITATIONS}

Perhaps the most important limitation of this systematic review is the theoretical aspects of these estimates. There is a significant amount of controversy around this issue and future research will hopefully answer this question. Similarly, the effective doses that are used in reports are estimates developed by mathematical programs. Furthermore, can these estimates be applied to the pediatric population in the 21\textsuperscript{st} century. As I already said, the Japanese cohort was severely malnourished and their dietary intake was subsidized with various non-food items.
These children were barely able to stay alive and very unlikely to have antioxidants in their diet that would protect them from the harms of radiation. Diets in the 21st century, in developed countries (which are the ones that use the majority of CT), are full of nutritious food high in antioxidants. Furthermore, we can not discount the idea that there was something different about the Japanese cohort that made them more susceptible to the harms of radiation. There are too many other confounding factors that could have lead to the increased risk of cancer after the two atomic bombs were dropped. Finally, it is also possible that the linear no-threshold assumption does not apply to radiation. Perhaps the harm can be less or more than linear especially in radiosensitive people. Unfortunately, there will be no answers to these questions in the near future. Therefore we have to believe these estimates and work with the health care community to minimize the potential risks from radiation. Further research, as outlined in this paper, will be expensive and time consuming but will tell us the true risk if any. We should be skeptical of any retrospective cohort study that aims to answer this question because of recall bias and exposure ascertainment bias.

FINAL THOUGHTS

A point should be made that there is a lack of pediatric radiologist and that this may be a public health concern. Last year there were only nine pediatric radiology fellows that graduated from fellowship programs (Molina P, personal correspondence). Pediatric radiologists are in tremendous need and are best equipped to prevent unnecessary tests from being run that could possibly have harmful affects. The communication between the pediatric practitioners (PCP and surgeons) and pediatric radiologists is very important. Through such communication the practitioners will learn about appropriate tests and will retain that information when dealing with similar clinical questions. As is seen in all interventions in public health, the greatest impact will
be seen by working from the ground up and by focusing more on the prevention. In this instance educating pediatric health care workers about the harms and about suitable alternative will have the greatest impact and will prevent unnecessary CT scans from being performed. The appropriate use of CT scanning in pediatric patients has the potential to be a primary cancer preventative strategy.

There have already been significant improvements in the area of scanning parameters used on pediatric patients as a recently shown. Unfortunately, this study sampled pediatric radiologists who have been pushing for the changes to happen for some years. A lot remains to be accomplished in the community hospitals where adult radiologists also perform scans on pediatric patients and where more education of physicians, both radiologists and pediatricians, will benefit the patients. Furthermore, the Image Gently campaign will greatly benefit the community and will hopefully reach out to adult radiologists in the community centers. The basic premise is that “one size does not fit all”. We should not be scanning a 2 year old child like an adult. Further, we should not scan a 2 year old child with the same settings as those of a 15 year old child. Finally, a 15 year old child who weighs 100 pounds should be scanned at a lower radiation dose than a 15 year old child who weighs 200 pounds.

Much has been done to protect our children. Nevertheless, millions have already been exposed at the adult doses for a couple of decades. These individuals who are now getting into their adulthood may be more likely to develop radiation induced cancer. Primary care physicians should be aware that there is a small, but not insignificant, chance that their patients could develop cancer that is not associated with lifestyle or diet choices but rather with previous radiation exposures. Such a rational is not meant to cause a wide spread panic but rather an awareness. We need to continue to advocate for lower use of mAs and kV settings in the
scanning of pediatric patients. More importantly, we need to minimize unnecessary CT scans. It may not be a wise strategy from business prospective, but business should never come before a child’s life. Dr. Frush has put it nicely when he said “we radiologists must be governed by what is good for children, not by what is good for business”. Even if patients, who develop radiation induced cancer, do not die from the disease there are significant morbidity concerns that have to be dealt with. Also, it is hard to quantify the social, psychological, and economic consequences of cancer. Until we know exactly what the risks are we should continue to believe in the current estimates. Therefore we should adhere to the principles set forth in this paper and in many others: minimize unnecessary exams, adjust the settings, replace exams by ultrasound or MRI, and educate future physicians about the harms of radiation.
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