The Risk of Cancer from CT Scans and Other Sources of Low-Dose Radiation: A Critical Appraisal of Methodologic Quality

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Abstract

Introduction: Concern exists that radiation exposure from computerized tomography (CT) will cause thousands of malignancies. Other experts share the same perspective regarding the risk from additional sources of low-dose ionizing radiation, such as the releases from Three Mile Island (1979; Pennsylvania USA) and Fukushima (2011; Okuma, Fukushima Prefecture, Japan) nuclear power plant disasters. If this premise is false, the fear of cancer leading patients and physicians to avoid CT scans and disaster responders to initiate forced evacuations is unfounded.

Study Objective: This investigation provides a quantitative evaluation of the methodologic quality of studies to determine the evidentiary strength supporting or refuting a causal relationship between low-dose radiation and cancer. It will assess the number of higher quality studies that support or question the role of low-dose radiation in oncogenesis.

Methods: This investigation is a systematic, methodologic review of articles published from 1975–2017 examining cancer risk from external low-dose x-ray and gamma radiation, defined as less than 200 millisievert (mSv). Following the PRISMA guidelines, the authors performed a search of the PubMed, Cochrane, Scopus, and Web of Science databases. Methodologies of selected articles were scored using the Newcastle Ottawa Scale (NOS) and a tool identifying 11 lower quality indicators. Manuscript methodologies were ranked as higher quality if they scored no lower than seven out of nine on the NOS and contained no more than two lower quality indicators. Investigators then characterized articles as supporting or not supporting a causal relationship between low-dose radiation and cancer.

Results: Investigators identified 4,382 articles for initial review. A total of 62 articles met all inclusion/exclusion criteria and were evaluated in this study. Quantitative evaluation of the manuscripts' methodologic strengths found 25 studies met higher quality criteria while 37 studies met lower quality criteria. Of the 25 studies with higher quality methods, 21 out of 25 did not support cancer induction by low-dose radiation (P = .0003).

Conclusions: A clear preponderance of articles with higher quality methods found no increased risk of cancer from low-dose radiation. The evidence suggests that exposure to multiple CT scans and other sources of low-dose radiation with a cumulative dose up to 100 mSv (approximately 10 scans), and possibly as high as 200 mSv (approximately 20 scans), does not increase cancer risk.

Introduction
Background
There is little doubt that the advent of computerized tomography (CT) and other diagnostic radiologic imaging has revolutionized the practice of medicine; CT scans have

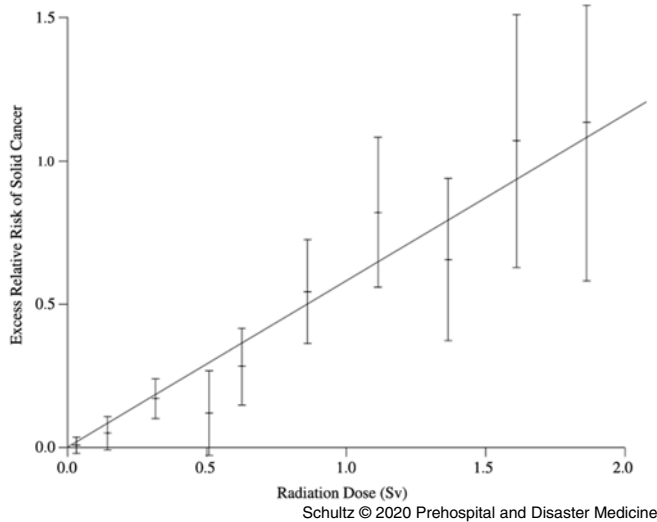Schultz © 2020 Prehospital and Disaster Medicine

Figure 1. Linear-No-Threshold (LNT) Model.
Note: Relationship between increased cancer risk and radiation dose as reported by the "Health Risks from Exposure to Low Levels of Ionizing Radiation on: BEIR VII – Phase 2" report with 90% confidence bars. (Graph created by Stephen David Williams using the numbers reported in the BEIR report. Used with permission.)

essentially become ubiquitous in the United States, where approximately 74 million scans were performed in 2017.[1] While this imaging technique offers benefits, the potential cancer risk associated with these studies remains controversial. If the wide-spread use of this technology is really inducing thousands of future cancer deaths, as suggested by Brenner, Berrington de Gonzalez, Smith-Bindman, and others, then the restrictive clinical guidelines being recommended by multiple organizations would be justified to protect the general population.[2–4] However, if the risk is inaccurately represented, then the mandate to reduce CT scanning regardless of indication may not be rational. It is imperative that clinicians, as well as the public, understand the risks and benefits of diagnostic studies used in everyday practice. Therefore, an objective analysis of the evidence to date is necessary to evaluate the risk of cancer from CT scans.

To help understand the approach used in the following investigation, some background information is needed. For general purposes, when quantifying radiation exposure, the units of measure used are the Sievert (Sv) and Gray (Gy). The Sv quantifies the amount of damage done to the human body while the Gy is the energy absorbed in the body per unit mass. For both x-rays and gamma rays, the two units of measure are numerically equivalent (ie, one Gy of radiation dose causes one Sv of damage). In addition, both gamma rays and x-rays are thought to behave the same within human tissue, causing equivalent injury. Therefore, cancer studies involving either entity apply to both. The dose from a single CT scan ranges from two millisieverts (mSv) to 20 mSv, with an average of two mSv per head CT and 10 mSv per CT scan of the abdomen and pelvis. As a comparison, most Americans receive three mSv per year from natural background radiation sources.[5]

The most important study in estimating the cancer risk from radiation exposure is the continuous long-term follow-up investigation of Japanese survivors from the atomic bombs

dropped on Hiroshima and Nagasaki in 1945. This longitudinal study is known as the Life Span Study, or LSS. In this Japanese population, cancer mortality and incidence have been studied as a function of radiation dose. Periodic reports on the data from this study are published by the Radiation Effects Research Foundation (Hiroshima, Japan).[6] The health effects of radiation have been reviewed and published periodically by the Biological Effects of Ionizing Radiation Committee, or BEIR, of the National Academy of Sciences (Washington, DC USA), with the latest iteration of the report being BIER VII in 2006.[7]

Since the first assessments of cancers in LSS participants, the analyses have reported a linear relationship between cancer incidence/mortality and increasing radiation dose when examining exposures of approximately one Gy and above. A report published in 2012 analyzing LSS data from 1950–2003 used a linear quadratic approach but asserts a similar overall relationship.[8] However, a separate evaluation focused on the cancer risk at lower doses that did not rely on the linear model, especially at 200 milligray (mGy) and below, was not performed.

Due to the observed linear relationship at higher doses, and the potential for large errors in estimating excess cancer risk at low-doses, the authors of the serial BEIR Committee reports have extrapolated the observed linear relationship between radiation dose and excess cancers to apply to all doses. This approach has led to the linear-no-threshold (LNT) model relating cancer risk to exposure, illustrated in Figure 1. While this figure is derived from earlier data, it depicts the concept. The theory states that any amount of radiation increases cancer risk and no safe level of exposure exists. In other words, no threshold exists below which radiation exposure does not cause cancer. This concept of a linear relationship between cancer risk and radiation dose across all exposure levels has essentially been used for estimations of health risks from radiation for the last 60 years. Calculations of cancers caused by radiation exposure and safety limits for exposed populations were all derived from the LNT model.

Importance
For the first few decades after the model was proposed, little reason existed to challenge it. Only a minute segment of the population was at-risk for significant radiation exposure. All this changed with the invention of the CT scan in 1972, and the exponential rise in its utilization since. Now, very large segments of the population are receiving higher radiation exposures, and the potential risk of cancer in the dose range of 100–200 mSv has become a very important issue. Recent publications have reached conflicting conclusions with respect to the cancer risk from low-dose exposure, resulting in intense debate regarding the validity of the LNT model.[8,9] As such, the presence or absence of a threshold exposure limit for radiation-induced cancer has become a critical issue for the medical community and the public. Significant effort and progress have been made by the medical community to reduce radiation exposure, as documented by the National Council on Radiation Protection 160 (Bethesda, Maryland USA) and benchmarks such as the American College of Radiology's (Reston, Virginia USA) CT Dose Registry.

The latest analysis of the LSS data published by Grant, et al in 2017 only fuels the debate. Investigators demonstrated a threshold for cancer risk in men below 100 mGy.[9] However, the authors were unable to make firm conclusions stating: "Findings from the current analysis regarding the dose-response shape were not fully consistent with those previously reported, raising unresolved

INCLUSION CRITERIA
Adults and children
Low-dose radiation defined as 200 mSv or less
Studies published from 1975 through 2017
English language
Randomized controlled trials (and meta-analysis), cohort studies, case control studies
External x-ray or gamma radiation exposure from diagnostic, environmental (including atomic bomb Survivors), or occupational sources
Studies where radiation exposure is either measured directly or estimated using current equipment and accepted methods where number and type of exposures are documented in a verifiable dataset
EXCLUSION CRITERIA
Animal studies
High-dose exposures, to include therapeutic radiation
Prenatal and preconception exposures
Articles addressing radiation effects on cells (adaptive response and bystander effects), chromosomes, biochemistry, or other non-organism targets
Review articles, abstracts, or editorials
Articles measuring calculated or estimated cancers based on modeling of exposure risk
Substantial exposure from internal contamination (excluding radon)
Studies of patients with previous history of cancer
Studies examining radiation impact on other diseases besides cancer such as meningiomas, cardiovascular disease, or mental health
Studies using surveys/questionnaires, number of procedures performed, or other indirect markers for actual radiation exposure

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Table 1. Article Inclusion and Exclusion Criteria

questions. At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies."[9] Nonetheless, the authors supported the use of a linear approach to data analysis consistent with the LNT model.

It is difficult to digest the large amount of data available and the conflicting conclusions stated in these publications. The authors considered using a meta-analytic approach for evaluating study outcomes but rejected it. All the investigations of human low-dose radiation exposure in the world's literature involve only cohort or case control studies. No prospective randomized trials exist. Cohort and case control studies are considered less robust designs, making meta-analysis of their results of questionable value. While some cohort and case control studies follow appropriate design rules, many are poorly constructed and highly flawed. As such, applying meta-analytic techniques to this mixture will yield results heavily confounded by lack of controls, poor study design, and flawed statistical evaluations. The resulting odds ratios and confidence intervals would have, at best, weak validity and at worst, be completely meaningless. In addition, the value of combining such studies is questionable. Given many involve different populations, outcome measures, sources of radiation, duration of exposure, sample size, and length of follow-up, the measurement of their heterogeneity would be very high, further compromising the validity of any findings.

It might be possible, however, to approximate an answer by identifying all the case control and cohort studies that more rigorously adhere to sound methodological design (utilize higher quality methodologies) and determine the number that either support or do not support the hypothesis that low-dose radiation causes cancer. A large preponderance of such investigations that endorse one or the other perspective would provide useful guidance.

Study Objective
Toward this end, the authors proposed examining the methodologic quality of investigations evaluating low-dose radiation and cancer induction published from 1975 through 2017. The articles' methodologies are scored using two separate tools to create a quantitative assessment measuring the strength of study design and identifying higher quality investigations. This will permit direct comparison between the number of studies using higher quality methodologies supporting cancer induction by low-dose radiation, and those refuting it, allowing assessment of the risks of cancer from low-dose radiation.

Methods
Study Design and Article Selection
Following the PRISMA guidelines, a systematic search was conducted in MEDLINE/PubMed (US National Library of Medicine, National Institutes of Health; Bethesda, Maryland USA); Scopus (Elsevier; Amsterdam, Netherlands; which includes coverage of EMBASE); Web of Science (Thomson Reuters; New York, New York USA); and the Cochrane Library (The Cochrane Collaboration; London, United Kingdom) for studies published in English from January 1975 through October 2017 evaluating the risk of cancer from low-dose radiation. The authors began the review in 1975 to allow sufficient time after the 1972 invention of the CT scan for research publications to appear that might include the device. A professional health sciences librarian (LM) designed and conducted the initial search on PubMed, and then applied the search strategy (Appendix A; available online only) to subsequent selected databases. All search results were imported into EndNote (Clarivate Analytics; Philadelphia, Pennsylvania USA), wherein duplicate studies were removed. For the search string, low-dose was defined as less than 200 mSv for the purposes of article inclusion. The current definition of low-dose is up to 100 mSv; however, the authors wanted to ensure identification of all potential studies.[10] In addition, articles investigating low-dose radiation were not restricted to diagnostic medical devices. Analyses of low-dose gamma radiation, such as studies examining cancer rates in nuclear power industry workers or those exposed to elevated levels of background radiation, were included. Other publications from government and regulatory agencies were added as well, as those identified from selected article bibliography reviews conducted manually by the authors.

Eligibility Criteria for Inclusion
To be included in the study, articles had to address the potential role or impact of low-dose gamma or x-ray radiation on the risk of developing any type of cancer. A list of article inclusion and exclusion criteria are contained in Table 1. First, two reviewers (CHS and RF) independently screened the titles and abstracts based on the criteria in Table 1. If this evaluation suggested the publications were potentially eligible for inclusion, the same reviewers examined the full-texts to make a final determination.

If the two reviewers disagreed regarding study eligibility, differences of opinion were resolved by consensus. Any persistent disagreement was resolved by a third independent reviewer (MD). For datasets with multiple publications that serially evaluated the same population over time, only the most recent publication was considered for inclusion in the study.

Measurements or Key Outcomes
After identifying the final set of articles, the methodology of each paper was independently scored by two reviewers (CHS and RF) using two separate tools to determine the quality of the research approach. Reviewers used a scoring template to reduce inconsistency. The first tool is the Newcastle Ottawa Scale (NOS) initially created by George Wells, PhD.[11] In an extensive review of approaches used for evaluation of non-randomized studies, 194 tools were identified that could be or had been used to assess such trials. Of these, only six were found to be suitable for systematic reviews, with the NOS being one.[12] The NOS was chosen as it is specifically designed to evaluate the methodologies of cohort and case control studies, has been in use for over 15 years, and is frequently referenced in the emergency medicine literature. It scores articles on a range of zero to nine based on evaluations in three categories: (1) Selection of cases/controls or cohorts; (2) Comparability of case/controls or cohorts based on design; and (3) Exposure or Outcome (Appendix B; available online only). Articles with scores of seven or greater were considered higher quality, given that most authors using the NOS identify this number as the lower limit characterizing good studies. However, the NOS does not evaluate all methodological aspects. To capture potential weaknesses the NOS misses, a second tool is required to fully characterize the studies by examining data analysis. This tool was developed by the authors and adapted from established resources in research methodology (ie, statistics texts and review articles). It identifies 11 lower quality indicators that are used to score the studies. Examples of these indicators include use of 90% confidence intervals, one-tailed T tests, failure to address confounding variables or predisposing factors, and no adjustment for multiple comparisons (Appendix C; available online only). An article found to contain two or fewer indicators is considered higher quality, mirroring the NOS that allows a reduction of up to two points for higher quality methodologies. An article's methodology was considered higher quality if: (1) it scored seven or more on the NOS, and (2) it contained two or fewer lower quality indicators. Failure to meet both metrics resulted in a study's methodology evaluated as lower quality. After independent scoring of all articles, both reviewers compared their results to reach consensus.

For meta-analytic studies, the NOS is not appropriate. To score these investigations, the authors used the Quality Assessment of Systematic Reviews and Meta-Analyses developed by the National Institute of Health's (Bethesda, Maryland USA) National Heart, Lung, and Blood Institute. This tool evaluates eight criteria as present or absent and yields a rating of good, fair, or poor.[13] Articles containing a minimum of six criteria were considered higher quality, to maintain consistency with the other scoring tools. The lower quality indicator tool was applied to these studies without modification. Only one article required assessment using this tool.

Data Analysis
The articles were then divided into two groups: those supporting the risk of cancer from low-dose radiation, and those that did

not. Investigators determined the support status by examining the conclusion section of the abstract, and when necessary, the conclusion section in the manuscript. The conclusion had to state or imply that all doses of radiation were associated with increased cancer risk. In some studies, the data reported in the results potentially contradicted the authors' conclusions. For the purposes of this investigation, however, the authors' statements were used to characterize the article. This same approach was used for studies that found an increase in some cancers but not others. Articles identified as not supporting the risk of cancer had to demonstrate a threshold for cancer induction at some level up to and including 100–200 mSv, and that increased cancer rates were not observed or existed only above the threshold value. Finally, the number of higher quality articles supporting or not supporting cancer induction by low-dose radiation was counted, and the difference between the two groups was evaluated using a chi-squared test for independence (Stata, Statacorp; College Station, Texas USA) with a P value of less than .05 considered significant. Since the study involved only de-identified data, the research team was not required to obtain Institutional Review Board approval.

Results
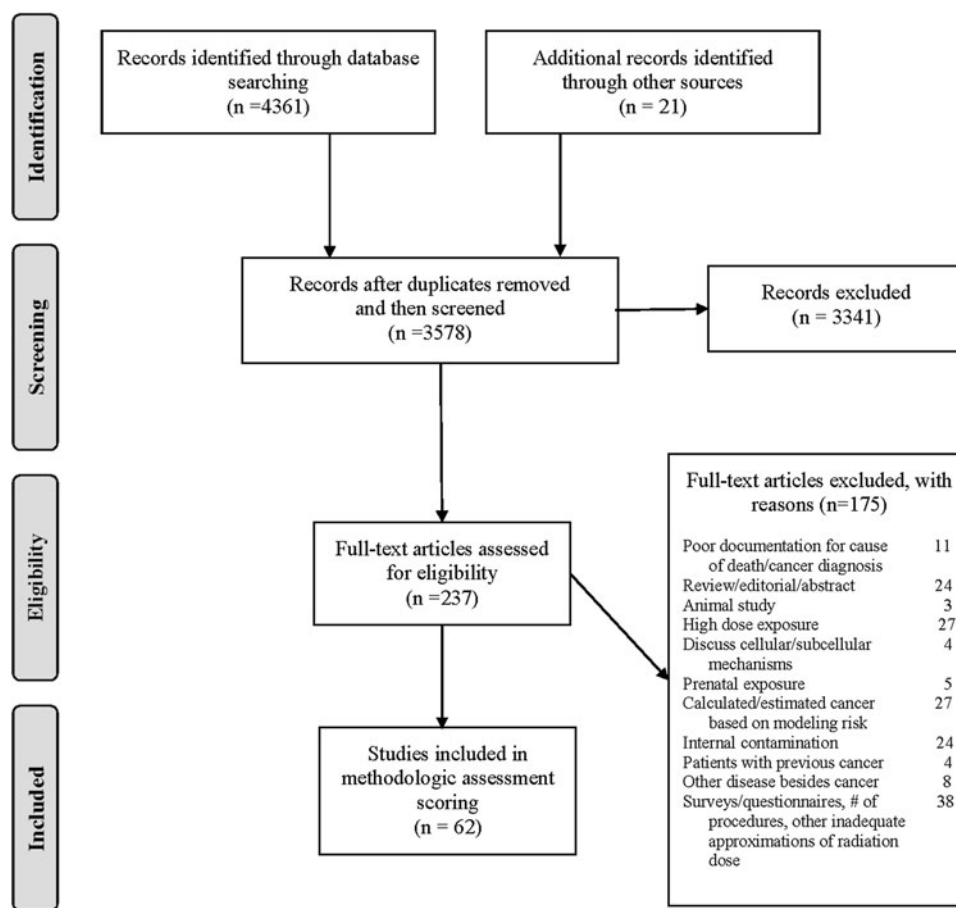*Characteristics of Selected Articles*
The literature search identified 4,382 potential articles for consideration: 4,361 retrieved from electronic databases and 21 obtained from bibliography reviews. After removal of duplicates, 3,578 publications remained. Initial screening of titles and abstracts reduced the number of articles further to 237. Detailed, independent full-text review of these remaining publications resulted in identification of 62 articles for inclusion in the study. Consensus was reached on all articles except one, which required intervention by a third author to adjudicate its disposition. A detailed graphic representation of the process following the PRISMA guidelines is listed in Figure 2.

Main Results
After evaluating and scoring the methodologic quality of all 62 articles, researchers identified 25 articles as utilizing higher quality approaches (Table 2[9,14–37]) and 37 characterized by lower quality approaches (Table 3[38–74]). These were fairly evenly divided with 27 articles endorsing cancer induction by low-dose radiation and 35 rejecting it. Examining the 25 higher quality methodology publications, the authors found 21 did not support the risk of cancer from low-dose radiation and four supported it. Using a chi-squared test for independence, this finding was significant with P = .0003. The only publications to receive perfect scores on the two methodologic evaluations both did not support cancer risk. For investigations using lower quality methodologies, 23 supported cancer induction while 14 rejected it. Details of the scoring evaluation for each article are found in Appendix D (available online only).

Discussion
The initial possibility that radiation might increase mutations, and subsequently the risk of cancer, was raised by the work of HJ Muller, published in 1927.[75] He demonstrated a linear increase in fruit fly mutations with exposure to rising doses of x-rays, but used only high doses with the lowest dose being four Gy. A later study performed by Spencer during the Manhattan Project showed a similar linear relationship of mutations to radiation dose for short-duration exposures, but did not expose the fruit flies to low-dose radiation, stopping at a dose of 250 mGy.[76] The influence

Figure 2. PRISMA Flow Diagram of Study Selection.
Note: Chart depicting the process of reviewing and selecting eligible articles from literature search for subsequent methodologic scoring. (From: DOI: 10.1371/journal.pmed.1000097.)

of the Spencer investigation, in combination with the advocacy by Muller and others, resulted in the formal acceptance of the LNT model (all radiation causes cancer and the risk increases as a linear function of increasing radiation dose) by the National Academy of Sciences Genetics Panel on the Biological Effects of Atomic Radiation (BEAR I Committee, later to become the BEIR Committee) in 1956.[77]

This linear model has remained the pivotal explanation for the relationship between radiation and cancer. The entire premise behind articles such as the one by Brenner, et al and others, that CT scans are causing cancer, is based on this model.[2,3] If this model is false, however, his estimate that possibly as many as 1.5% to 2.0% of all cancers in the United States are caused by CT scans would be wrong. The purpose of this study was to examine the methodologic strengths of the literature and determine if the evidence from investigations using higher quality case control and cohort study methodologies supports or does not support the risk of cancer from low-dose radiation.

Researchers identified only four out of 25 studies characterized by higher quality methodologies that endorsed a risk of cancer from low-dose radiation. While no standard exists that can absolutely indicate when a sufficient quantity of higher quality studies has been performed to change practice, one can consider a change if the clear preponderance of these studies suggests a new

direction is indicated. In this analysis, 21 out of 25 investigations characterized as using higher quality methodologies demonstrated the existence of a threshold for cancer induction. These studies demonstrated no increased cancer risk for individuals experiencing radiation exposures up to at least 100 mGy, and possibly as high as 200 mGy.

The authors acknowledge that attempting a quantitative analysis of methodologic quality will incorporate a certain amount of subjectivity. No tool currently available can completely eliminate this risk. However, significant guidance on use of the NOS exists, including structured scoring tools that can increase consistency in evaluations. These data collection sheets were employed throughout the entire evaluation (Appendix E; available online only). In addition, the use of the lower quality indicator tool to supplement the NOS provides a method of evaluation that is less subject to interpretation and more objective. This second evaluation tool is needed because the NOS does not evaluate how data are analyzed. Even if a study received a perfect score on the NOS, it can still have significant weaknesses in the way data are evaluated. Common errors such as use of 90% confidence intervals (CIs), failure to control for reverse causation, and failure to adjust for significant predisposing factors beyond the two that are addressed in the NOS all can result in lower quality methodologic approaches. These are the types of indicators used to create the second tool.
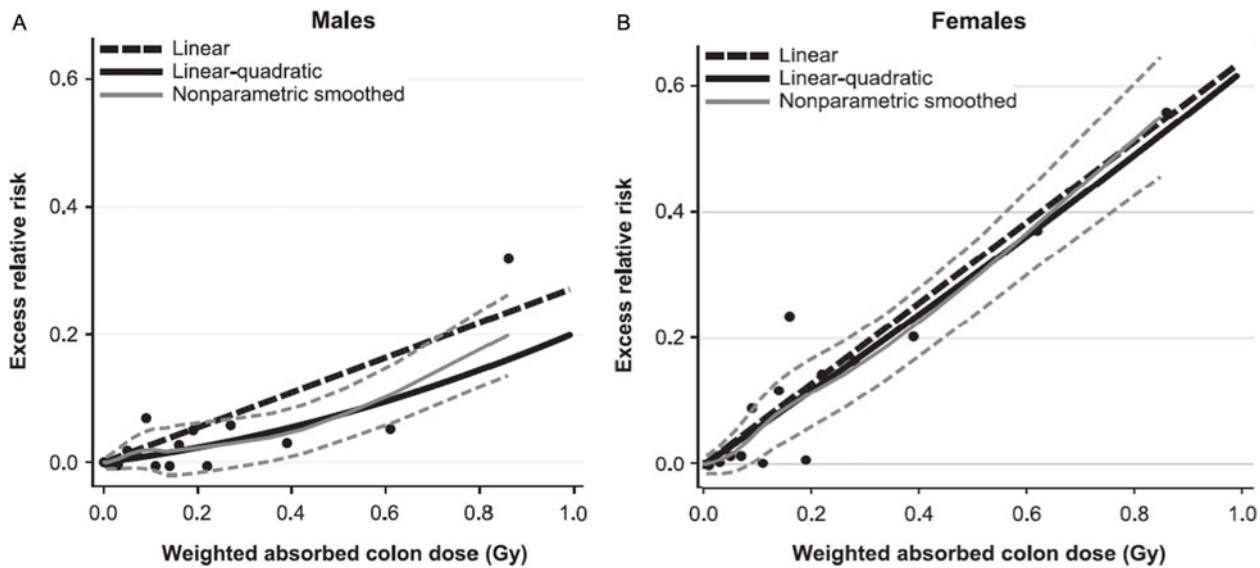
Figure 3. Cancer Risk for Males and Females as a Function of Increasing Radiation Exposure Up to 1 Gy.
Note: Panels A and B: Solid cancer dose-response functions for males and females (0–1 Gy). Fitted linear (black dashed line) and linear-quadratic (black solid curve) ERRs for all solid cancers using linear and linear-quadratic dose-response functions for males and females over the range of 0–1 Gy. Also shown are ERR estimates for 15 visible dose categories (points) and a nonparametric smoothed estimate (solid grey curve) with point-wise 95% CIs (dashed grey curves). The ERRs are given for subjects at attained age of 70 years after exposure at age 30 years. (Used with permission; copyright 2018 Radiation Research Society).

To improve transparency, the individual scores for all articles are included in Appendix D (available online only), so readers can assess the study methodology evaluations for themselves.

Evaluation tools such as Grades of Recommendation, Assessment, Development, and Evaluation and others were not used for this study. They lack sufficient granularity to address the wide-range of study designs and subjects involved. As essentially none of the articles reviewed were randomized, controlled, prospective studies, they all would receive lower marks. This makes discrimination between cohort and case control studies using higher and lower quality methodologies difficult. Given all but one included article was either a case control or cohort study, investigators needed evaluations tools that would be effective in scoring these papers. That is why researchers selected the NOS and Lower Quality Indicator Scale.

The most widely cited data supporting the hypothesis that all radiation causes cancer comes from analysis of the LSS. While the data collected in this study are accurate, the linear and linear quadratic interpretation of the relationship between radiation and cancer across all levels of exposure is potentially flawed. In the latest examination of the LSS data by Grant, et al, a linear or curvilinear relationship does exist between increasing doses of radiation and an increased risk of cancer starting above 200 mGy.[9] However, as one moves down the graphic line to lower doses of radiation below 200 mGy, a clear risk of increased cancer induction disappears. The graphs depicting the relationship between absorbed dose and cancer risk illustrate this observation (Figure 3). The dashed line illustrating the lower bounds of the 95% confidence interval for excess relative risk for cancer in men remains below zero until past 200 mGy, while that for women does not become positive until past 100 mGy.[9] This fairly clearly suggests the possibility of a threshold for cancer risk if these data were evaluated as a separate entity rather than in totality with all the

other data. Indeed, the conclusion of this latest LSS study shows no increased cancer risk in men for doses up to 100 mGy (excess relative risk of 0.010 with 95% confidence intervals of −0.0003 to 0.021).[9]

It appears possible that two separate phenomena occur across the range of radiation exposure; one manifesting at low doses (100 mSv, possibly extending to 200 mSv) and a second process manifesting at higher doses. This is similar to the impact of sunlight on the human body. Low doses of ultraviolent radiation create vitamin D3 without causing significant skin damage. High doses will cause sunburn and increase the risk of skin cancer. Applying this concept, researchers would need a new objective model that could depict both processes while making no assumptions about the data. In fact, such models exist. Doss, et al used a regression approach in which the radiation dose in Gy was entered into the model using a restricted cubic spline transformation with four knots. This method of data analysis is flexible and allows the line of best fit to cross the Y axis at any location and also allows for negative predicted excess relative risk values. When this model is applied to the data from a previous analysis of the LSS, the 95% CIs for line of best fit are below zero for doses under 200 mGy, clearly demonstrating the possibility of a threshold.[78]

Sasaki, et al, concerned about the same issue of constrained data analysis, used a different approach. They employed an artificial neural network to examine the relationship between radiation dose and cancer risk. This method can identify changes in the dose-response relationship and is not limited to one type of graphical representation, allowing the line of best fit to follow the data. Using this model, the authors also identified a threshold effect, with no increased risk for radiation-induced cancer below 100–200 mSv.[22]

It might be useful to illustrate the difference found between studies using higher quality and lower quality methodologies by

describing several investigations involving the risk of cancer from workplace radiation exposure from sources used to generate nuclear power. Studies concluding no cancer threshold exists suffer from significant flaws, including the use of spurious data, 90% confidence intervals, one-tailed tests of significance, and outcome measures that obscure the presence of a low-dose threshold, such as increased cancer risk per Gy or use of a restricted linear approach for data representation.[43,44,55,79] Re-analysis of a study using information on occupational radiation exposure in the nuclear power industry from 15 countries that initially found a significant increase in cancer risk from low-dose exposure found no significantly increased risk after spurious Canadian data were excluded.[21] In contrast, the Johns Hopkins School of Public Health (Baltimore, Maryland USA) conducted a study of cancer incidence in nuclear shipyard workers. This investigation was a rigorously performed search for health risks of radiation to civilian employees of eight shipyards that overhauled and repaired nuclear-propelled US Navy ships and submarines. They compared cancer rates experienced by badged nuclear workers servicing nuclear powered vessels who had exposure to low radiation doses with their colleagues who did not enter the radiation areas and so were not exposed to the low radiation doses. This eliminated any impact from the "healthy worker effect" (the phenomenon that employed individuals are healthier than the general population and so comparisons between the two can lead to inaccurate results). The authors used 95% confidence intervals and non-linear restricted methods of data analysis, addressed such confounders as socio-economic status, and stratified worker analysis by radiation dose. These investigators found no increased risk of cancer from exposure to low-dose radiation.[33]

Limitations

Several limitations exist that potentially impact the study results. First, quantitative evaluation of methodologic quality incorporates a certain degree of subjectivity. Some criteria are difficult to objectively describe and so variability can occur in the quantification process. Investigators minimized this by using a scoring template that helped reduce inconsistency and by requiring consensus for each score. Second, the study authors performed the quantitative analysis. While it would be desirable to use another group blinded to the study's goal, it was not possible to find other emergency physicians that were unbiased. All the physicians contacted candidly admitted either a bias for or against the concept that all radiation causes cancer. None honestly believed that a state of equipoise could exist for either outcome. The authors were the only emergency physicians identified that believed that both outcomes were possible. Since scoring bias could not be completely eliminated, the raw scores for all 62 articles are included in the appendix so readers can assess the scoring accuracy for themselves. Third,

some studies, if only modestly-powered, may have failed to identify a significant risk of cancer at lower doses due to the difference in the effect size. If there was a significant, but small, association between low-dose radiation and cancer, this might have required a larger sample to detect than associations at higher doses, reflecting a Type II error. However, this is unlikely as most studies included participants in the tens of thousands. In addition, the LSS just reported no evidence for cancer at doses below 100 mSv in men, after reporting just the opposite for decades. This change reflects results from a now adequately powered study. Fourth, some studies may have yielded data that may not have easily fit within the binary outcomes of "support" or "not support." However, only three of the 62 articles produced mixed results, and none of these were in the higher quality study group. Even for these investigations, the authors' conclusions easily placed them into one of the two categories. Fifth, the authors analyzed studies documenting chronic exposure and acute intermittent exposure together. Very limited data exist quantifying the difference between cumulative low-dose exposure and single dose. Given the majority of studies evaluating both exposure types found no increased cancer rates, this is less likely to impact the results. Lastly, the lower quality indicator tool has not been used previously. Nonetheless, all 11 criteria are well-known, validated methodology flaws and are documented in research design textbooks and multiple review articles. It would seem difficult to argue that the results from studies with methods containing three or more of these known flaws could produce a meaningful evaluation.

Conclusion

This investigation demonstrates that a preponderance of studies using higher quality case control and cohort methodology support the existence of a threshold for cancer induction by radiation up to a dose of 100 mSv, and possibly as high as 200 mSv. These findings suggest that the cancer risk from this radiation dose is minimal and exposure to at least 10 CT scans, and possibly as many as 20, is unlikely to cause cancer.

Author Contributions

CHS, RF, and LS-LM are responsible for the conception and design of the study. LS-LM programmed the software to search the literature and provided data acquisition. Data analysis and interpretation was done by CHS, RF, and MD. Drafting and revision of the manuscript was performed by CHS, RF, LS-LM, and MD with all authors making substantial contributions. CHS takes responsibility for the manuscript content as a whole.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1049023X1900520X

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ARTICLES SUPPORTING CANCER INDUCTION BY LOW-DOSE RADIATION

Authors	Year	Total NOS Score	Low-Quality Indicator Score	Sample Size	Study Design	Exposed Population	Radiation Source	Outcome Measures	Follow-Up Length
Grant EJ, Brenner A[9]	2017	8	2	80,205	Cohort	Atomic bomb survivors	Atomic bomb	Solid cancers	51 years
De Gonzalez AB, Salotti JA[14]	2016	7	2	178,602	Cohort	Pediatric patients with CT scans	CT scans	Leukemia, malignant brain lesion	23 years
Huang WY, Muo CH[15]	2014	8	2	24,418	Cohort	Pediatric patients with head CTs	Head CT scans	Malignant/benign brain tumor	10 years
Daniels RD, Bertke S[16]	2013	8	1	1,845	Nested case control	US nuclear workers	Radio-nuclides, nuclear reactors	Leukemia mortality	54 years

ARTICLES NOT SUPPORTING CANCER INDUCTION BY LOW-DOSE RADIATION

Authors	Year	Total NOS Score	Low-Quality Indicator Score	Sample Size	Study Design	Exposed Population	Radiation Source	Outcome Measures	Follow-Up Length
Kitahara CM, Linet MS[17]	2017	8	2	110,297	Cohort	US radiologic technologist	Diagnostic medical radiation	Death from brain/CNS cancer	29 years
Krille L, Dreger S[18]	2015	8	1	44,584	Cohort	Pediatric patients with CT scans	CT scans	Leukemia, lymphoma, CNS tumor before age 15	15 years
Journy N, Rehel J-L[19]	2015	8	0	67, 274	Cohort	Pediatric patients with CT scans	CT scans	Cancer incidence before age 15	10 years
Socol Y, Dobrzyński L[20]	2015	8	1	86,661	Cohort	Atomic bomb survivors	Atomic bomb	All cancer mortality	53 years
Zablotska LB, Lane RSD[21]	2014	7	1	45,468	Cohort	Canadian nuclear workers	Radio-nuclides, nuclear reactors	All cancer mortality	38 years
Sasaki MS, Tachibana A[22]	2014	8	1	86,661	Cohort	Atomic bomb survivors	Atomic bomb	Occurrence of all cancers	50 years
Merzenich H, Hammer GP[23]	2014	8	1	8,972	Cohort	German nuclear power workers	Nuclear power plants	All cancer mortality	17 years
Cappa M, Cambiaso P[24]	2013	7	1	123	Case control	Patient < 18 months old with cardiac defects	Cardiac catheter-ization	Thyroid abnormality and cancer	24 years
Tao Z, Akiba S[25]	2012	7	2	31,604	Cohort	Citizens living in Yangjiang, China	Natural background radiation	Cancer and non-cancer deaths	20 years
Hammer GP, Blettner M[26]	2012	7	1	6,000	Cohort	Male German airline pilots	Cosmic radiation	Cancer mortality	44 years
Hammer GP, Seidenbusch MC[27]	2011	9	0	78,527	Cohort	German children under age 14.5	Conventional radio-graphic examination	Cancer incidence	26 years
Boice JD, Cohen S[28]	2011	9	2	46,970	Cohort	Rocketdyne employees	Nuclear reactors & fuel	Mortality analysis	60 years
Jeong M, Jin YW[29]	2010	7	1	16,236	Cohort	Male Korean nuclear power workers	Nuclear power facilities	Cancer incidence	14 years

Nair RRK, Rajan B[30]	2009	9	2	69,958	Cohort	People living in Karunagappally, India	Natural background radiation	Cancer incidence	15 years
Gun RT, Parsons J[31]	2008	7	2	10,983	Cohort	Male Australian participants in nuclear tests	Nuclear weapons tests	Mortality and cancer incidence	20 years
Yiin JH, Silver SR[32]	2007	7	1	4,388	Nested case control	Portsmouth Naval Shipyard workers	Nuclear powered ships and x-rays	Lung cancer mortality	45 years
Sponsler R, Cameron JR[33]	2005	9	0	70,730	Cohort	US Nuclear shipyard workers	Nuclear powered ships and x-rays	All-cause and cancer mortality	25 years
Howe GR, Zablotska LB[34]	2004	9	1	53,698	Cohort	US nuclear power workers	US nuclear power plants	Non-cancer and cancer mortality	18 years
Inskip PD, Ekbom A[35]	1995	8	2	968	Case control	Swedish citizens getting diagnostic medical x-rays	Medical x-rays for diagnosis	Thyroid cancer incidence	58 years
Boice JD Jr, Morin MM[36]	1991	7	2	2,481	Case control	US members of 2 prepaid health plans	Medical x-rays for diagnosis	Leukemia, NHL, multiple myeloma	27 years
Storm HH, Iversen E[37]	1986	7	2	479	Case control	Tuberculosis patients in Denmark	Chest fluoroscopy	Breast cancer incidence	40 years

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Table 2. *(continued).* Articles with Higher Quality Methodologies Characterized by Supporting or Not Supporting Cancer Induction by Low-Dose Radiation
Abbreviations: CNS, Central Nervous System; CT, Computed Tomography; NHL, Non-Hodgkin's Lymphoma; NOS, Newcastle Ottawa Scale; US, United States.

ARTICLES SUPPORTING CANCER INDUCTION BY LOW-DOSE RADIATION

Authors	Year	Total NOS Score	Low-Quality Indicator Score	Sample Size	Study Design	Exposed Population	Radiation Source	Outcome Measures	Follow-Up Length
Daniels RD, Bertke SJ[38]	2017	7	3	308,297	Nested Case-Control	Nuclear workers (French, UK, US)	Radio-nuclides, gamma ray, x-ray, neutron	Mortality from all solid cancers, leukemias	Average 27 years
Hsieh WH, Lin IF[39]	2017	7	4	6242	Cohort	Taiwanese building residents	Cobalt-60 (gamma ray)	All cancer	30 years
Wang F, Sun Q[40]	2016	6	4	7703	Case Control	Chinese medical x-ray workers	Medical x-ray	All cancer	315,309 Person-years
Preston DL, Kitahara CM[41]	2016	8	3	66,915	Cohort	US radiologic technologists	Medical x-ray	Breast cancer	1,089,502 person-years
Smoll NR, Brady Z[42]	2016	8	4	105,427	Cohort	Atomic bomb survivors	Atomic bomb radiation	Brain cancer	40 years
Richardson DB, Cardis E[43]	2015	7	4	308,297	Cohort	Nuclear workers (French, US, and UK)	Radio-nuclides, gamma ray, x-ray, neutron	All cancer mortality	8.2 million person years, median 26 years
Leuraud K, Richardson DB[44]	2015	7	3	308,297	Cohort	Nuclear workers (French, US, and UK)	Radio-nuclides, gamma ray, x-ray, neutron	Mortality from leukemia and lymphoma	8.22 million person-years
Schubauer-Berigan MK, Daniels RD[45]	2015	8	3	119,195	Cohort	Nuclear workers (US)	Radio-nuclides, gamma ray, x-ray, neutron	All cancer mortality	4,019,065 person-years
Mathews JD, Forsythe AV[46]	2013	6	2	680,211	Cohort	Australian Medicare patients	CT imaging	All cancer	Mean 9.5 years
Samartzis D, Nishi N[47]	2013	8	3	80,180	Cohort	Atomic bomb survivors	Atomic bomb radiation	Soft tissue sarcoma	2,170,732 person-years
Choi KH, Ha M[48]	2013	7	4	36,394	Cohort	Korean diagnostic radiation workers	X-ray	All cancer	Max 7 years, 159,189 person-years
Eisenberg MJ, Afilalo J[49]	2011	5	1	82,861	Cohort	Canadian cardiac patients	X-ray	All cancer	Mean 5 years
Ronckers CM, Land CE[50]	2010	8	4	5,513	Cohort	US Scoliosis female	X-ray	All cancer mortality	Mean 47 years, total 257,915 woman-years
Muirhead CR, O'Hagan JA[51]	2009	8	4	174,541	Cohort	UK Radiation workers	Radio-nuclides, gamma ray, x-ray, neutron	All cancer	3.9 million person-years
Zielinski JM, Garner MJ[52]	2009	5	5	67,582	Cohort	Canadian medical workers	Medical x-rays	Cancer mortality & incidence	36 years
Ronckers CM, Doody MM[53]	2008	6	3	3,010	Cohort	US scoliosis female	X-ray	Breast Cancer	118,905 total years, median 35.5 years

Authors	Year	Total NOS Score	Low-Quality Indicator Score	Sample Size	Study Design	Exposed Population	Radiation Source	Outcome Measures	Follow-Up Length
Cardis E, Vrijheid M[54]	2007	7	6	407,391	Cohort	15 country nuclear workers	Radio-nuclides, gamma ray, x-ray, neutron	All cancer mortality (cause specific)	5.2 million person-years
Cardis E, Vrijheid M[55]	2005	7	3	407,391	Cohort	15 country nuclear workers	Radio-nuclides, gamma ray, x-ray, neutron	All cancer mortality	5.2 million person-years
Matsuura M, Hoshi M[56]	1997	7	6	35,123	Cohort	Hiroshima prefecture atomic bomb survivors	Atomic bomb radiation	All cancer mortality	646,209 person-years
Howe GR, McLaughlin J[57]	1996	7	3	31,917	Cohort	Canadian Tuberculosis	Fluoroscopy (x-ray)	Breast cancer mortality	Mean 31 years
Cardis E, Gilbert ES[58]	1995	7	5	95,673	Cohort	Nuclear workers (US, Canada, UK)	Radio-nuclides, gamma ray, x-ray, neutron	All cancer mortality	2,124,526 person-years
Hoffman DA, Lonstein JE[59]	1989	6	5	1,030	Cohort	US scoliosis patients	X-ray	Breast cancer	Mean 26 years
NIH Quality Assessment Score for Meta-Analyses									
Jansen-Van Der Weide, MC[60]	2010	5 out of 8 possible criteria	2	7 studies; 30 to 5865 subjects	Meta-analysis	Women with genetic risk for breast cancer	Diagnostic medical x-rays	Breast cancer	Not stated to 20 years
ARTICLES NOT SUPPORTING CANCER INDUCTION BY LOW-DOSE RADIATION									
Authors	*Year*	*Total NOS Score*	*Low-Quality Indicator Score*	*Sample Size*	*Study Design*	*Exposed Population*	*Radiation Source*	*Outcome Measures*	*Follow-Up Length*
Ohira T, Takahashi H[61]	2016	4	4	300,476	Cross sectional	Persons age 0–18 living in Fukushima, Japan	External gamma radiation	Thyroid cancer	4 years
Lee T, Sigurdson AJ[62]	2015	6	4	65,719	Cohort	US radiologic technologists	Diagnostic medical x-rays	Basal cell carcinoma	55 years
White IK, Shaikh KA[63]	2014	6	1	104	Cohort	Children requiring CSF shunts	Head CT scans	Any cancer	10 years
Metz-Flamant C, Laurent O[64]	2013	8	5	59,021	Cohort	French nuclear workers	Neutrons, x-rays, and gamma rays	Any cancer, stroke, or CAD	36 years
Pogoda, JM, Nichols, PW[65]	2011	6	3	412	Case control	Adults living in Los Angeles	Diagnostic medical x-rays	Acute myeloid leukemia	7 years
Yuan, M-K, Chien, C-W[66]	2010	3	3	2,292	Case control	Cardiologists in Taipei, Taiwan	Radiation from fluoroscopy	Cancer, number of medical visits, cataracts, URIs	4 years
Vrijheid M, Cardis E[67]	2008	6	2	295,963	Cohort	Nuclear workers in 15 countries	X-rays and gamma rays	Chronic lymphocytic leukemia deaths	4.5 million person-years; 13-year average

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Table 3. Articles with Lower Quality Methodologies Characterized by Supporting or Not Supporting Cancer Induction by Low-Dose Radiation *(continued)*

ARTICLES SUPPORTING CANCER INDUCTION BY LOW-DOSE RADIATION

Authors	Year	Total NOS Score	Low-Quality Indicator Score	Sample Size	Study Design	Exposed Population	Radiation Source	Outcome Measures	Follow-Up Length
Lambe M, Hall P[68]	2005	6	2	23,097	Cohort	Sweden patients getting PTCA	Fluoroscopy	All cancer incidence	10 years
Zielinski JM, Garner MJ[69]	2005	5	2	42,175	Cohort	Canadian dental workers	Diagnostic dental x-rays	Cancer mortality & incidence	36 years
Engels H, Swaen GM[70]	2005	8	3	7,229	Cohort	Nuclear workers in Belgium	Neutrons, gamma rays	All cause and cancer mortality	25 years
Langner I, Blettner M[71]	2004	6	1	19,184	Cohort	European male airline cockpit crew members	Cosmic gamma radiation	All cause and cancer mortality	336,000 person- years; 36 years
Iwasaki T, Murata M[72]	2003	6	1	176,000	Cohort	Male nuclear workers in Japan	Gamma radiation	All cause and cancer mortality	10 years
Artalejo FR, Lara SC[73]	1997	6	1	5,657	Cohort	Spanish nuclear workers and miners	Gamma radiation	All cause and cancer mortality	38 years
Jablon S, Boice JD[74]	1993	5	2	9,132	Cohort	Workers at a US nuclear power plant	Gamma radiation	All cause and cancer mortality	20 years

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Table 3. *(continued).* Articles with Lower Quality Methodologies Characterized by Supporting or Not Supporting Cancer Induction by Low-Dose Radiation
Abbreviations: CAD, Coronary Artery Disease; CSF, Cerebral Spinal Fluid; CT, Computed Tomography; NOS, Newcastle Ottawa Scale; PTCA, Percutaneous Transluminal Coronary Angioplasty; UK, United Kingdom; URI, Upper Respiratory Infection; US, United States.