Paper

UPDATE ON LINEAR NON-THRESHOLD DOSE-RESPONSE MODEL AND IMPLICATIONS FOR DIAGNOSTIC RADIOLOGY PROCEDURES

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Abstract—**Cancer risk estimates are used in the setting of radiation protection standards by international and national organizations, and for this purpose need to be developed for low doses of radiation. The approach has involved extrapolation from cancer mortality and incidence values at higher doses to predict the low-dose estimates. Such an extrapolation has generally involved the use of the linear non-threshold (LNT) theory. Recent reports from the National Research Council (BEIR VII) and the International Commission on Radiological Protection (ICRP) have considered the appropriateness of the use of LNT for the purposes of radiation protection standard setting. The overall conclusion from both committees was that current scientific evidence remains consistent with the LNT hypothesis, while appreciating that this might not rule out the possibility that other extrapolation models might well be valid but require further evaluation and additional research to establish their validity. The dose and dose-rate effectiveness factor (DDREF) is used for adjustment in the extrapolation from high to low doses and from high to low dose rates. The BEIR VII committee proposed a new Bayesian approach for estimating DDREF and concluded that a value of 1.5 best fit the data. This is a departure from the previously used value of 2, which is still proposed by ICRP in its most recent recommendations. The current cancer risk estimation process as utilized by ICRP and BEIR VII is used here to assess the potential risks from annual whole-body computed tomography (CT) screens using information and an approach published by Brenner and Ellington. The major conclusion is that potential radiation risks need to be considered along with the pros and cons of the detection limits of the procedure and the impact of false positives.**

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Key words: National Council on Radiation Protection and Measurements; linear hypothesis; dose, low; computed tomography

INTRODUCTION

Cancer risk estimates for radiation exposures at low doses (<100 mSv) and low-dose rates have inevitably been based on extrapolation from epidemiological data on tumor incidence from higher doses (>100 mSv) and for acute exposures. For the purposes of radiation protection with an eye on being protective of public health, this dose extrapolation has been based on the theory that there is a linear non-threshold (LNT) relationship between tumor incidence and dose over the low-dose range. The aim of this short review is to provide the most recent views from several learned groups and committees on the validity of the LNT hypothesis in the context of radiation protection standards and cancer risk estimates. (The issues to be addressed in this review are demonstrated in Fig. 1.) The estimation of effects at low-dose rates from those available at higher dose rates is conducted through the use of a dose and dose-rate effectiveness factor (DDREF). The views of the International Commission on Radiological Protection (ICRP 2007) and the National Research Council's (NRC) Biological Effects of Ionizing Radiation (BEIR) Committee VII (NRC 2006) on the current best estimate of DDREF are also discussed. Clearly all approaches used for extrapolation, together with the human and animal tumor data available and new findings in the area of cellular and molecular biology, require constant reconsideration as new technologies and data become available. Thus, there are research needs that are identified that can ultimately reduce uncertainty in cancer risk estimates. Such needs are briefly identified. Finally, since this National Council on Radiation Protection and Measurements (NCRP) Annual Meeting concerns the uses of radiation in medicine, a short discussion of how the recent risk estimation approaches can be applied to computed tomography (CT) screening is presented. The issuance of any new report on radiation protection standards is really a snapshot in time, representing the use of the best available data and approaches at that time. Attention then needs to be applied to the next iteration.

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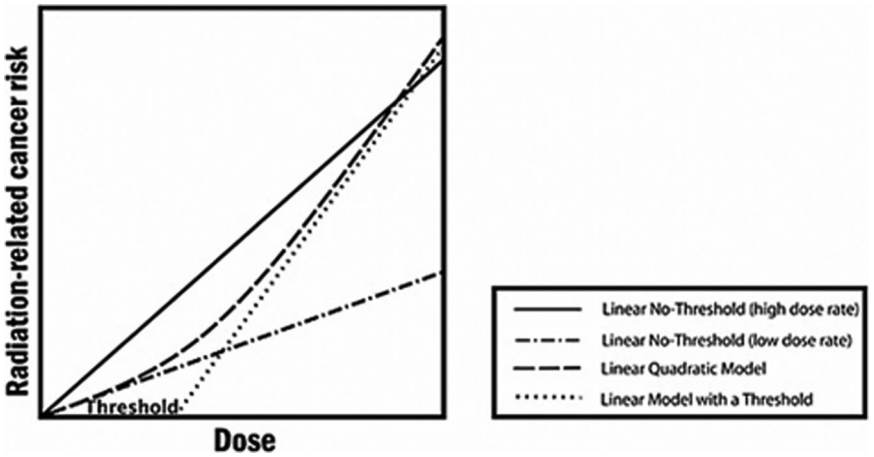

Fig. 1. Radiation-induced cancer risk as a function of dose for linear, linear-quadratic and threshold responses. The LNT response for a low-dose rate is compared to that for a high-dose rate. (From NRC 2006, with permission.)

WHAT'S NEW—RECENT REPORTS ON RISK ESTIMATION

Several recent reports have presented reviews of the most recent radiation biology and epidemiology data that can form the basis for the development of quantative cancer risk estimates and non-cancer dose-response characterization. The report developed by the BEIR VII Committee (NRC 2006) was based on their stated task of developing "the best possible risk estimate for exposure to low-dose, low linear-energy-transfer (LET) radiation in human subjects." The ICRP (2007) recommendations had a similar goal, namely, to take account of the most recent biological and physical information in the development of radiation protection standards. A third report developed by the French Academy of Sciences (Tubiana et al. 2005) presents a somewhat different view and relies on several non-targeted effects to define low-dose tumor responses. The current state of biological and mechanistic data that are used in support of extrapolation models for estimating low-dose, low-dose-rate cancer risks are reviewed in ICRP Report 99, *Low-Dose Extrapolation of Radiation-Related Cancer Risk* (ICRP 2005). The information contained in these reports is used herein for describing the current view of the role of LNT in extrapolation methodology.

LNT AS AN EXTRAPOLATION MODEL

Radiation cancer risk estimates are needed for estimating the lifetime risks of cancer resulting from any specified dose of ionizing radiation. The use (within the United States, for example) is to apply these estimates to exposure scenarios for groups within the population. In addition, these risk estimates are used to establish radiation protection standards and dose limits for the public and for occupationally exposed persons. They are used more indirectly for developing guidelines for patient exposures for radiotherapy and other medical procedures.

As in their previous reports, BEIR VII (NRC 2006) and ICRP (2007) have relied heavily on the data from the atomic bomb survivor studies, in particular the Life Span Study (LSS). In previous reports, BEIR and ICRP had relied on data set 1986 (DS86), which was, at the time, the most recent dose assessment. The current data set, DS02, was used in the BEIR VII (NRC 2006) and ICRP (2007) recommendations. DS02 was improved over DS86 by including the specifics of the radiation released by the bombs and the effects of shielding by structures and terrain. Preston et al. (2004) conducted an analysis of the effects of the recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. They concluded that the estimates of solid cancer radiation risk per Sv and the curvilinear dose-response for leukemia were both decreased by about 8% by the dosimetry revision, as a result of the increase in the gamma-ray dose estimates. In their analysis, there is an informative discussion of the effect of the extra 3 y of follow-up on the dose-response curve. There is a statistically significant upward curvature for solid cancers on the restricted dose range of 0–2 Sv (Preston et al. 2004). However, the authors clearly advise that "the low-dose slope of a linear-quadratic fit to the 0–2 Sv dose range should probably not be relied upon for risk estimation," because it is substantially smaller than that for other ranges (e.g., 0–1 Sv, 0–0.5 Sv, and 0–0.25 Sv).

The cancer risk estimates provided in these two recent reports (NRC 2006; ICRP 2007) were also based on cancer incidence as opposed to being based only on cancer mortality. The advantages of using incidence data are that nonfatal cancers are taken into account and diagnostic accuracy is generally enhanced. The estimates

of excess relative risk of solid cancers for Japanese atomic bomb survivors are shown in Fig. 2 (from BEIR VII) together with linear and linear-quadratic fits. However, it is important to note that even when these new data were incorporated into risk estimates, there was very little difference from previous BEIR and ICRP estimates. For detriment-adjusted cancer incidence, the new estimates (ICRP 2007) are very similar to those based on cancer mortality from previous BEIR and ICRP reports. Overall, for detriment-adjusted cancer incidence, the new ICRP estimates are 5.5% per Sv for the whole population and 4.1% per Sv for adults. For these estimates detriment for a tissue T is defined as:

$$D_T = (R_{F.T} + q_T R_{nF.T}) l_T$$

where R_F is the nominal risk of fatal disease, R_{nF} is the nominal risk of non-fatal disease, q is a non-fatal weight (between 0 and 1) reflecting the reduced quality of life associated with living with a serious illness, and l is the average life lost to the disease relative to normal life expectancy, expressed relative to the overall cancers. The quality of life factor is a function of the lethality of the disease and a subjective judgment accounting for pain, suffering and adverse effects of treatment.

In addition, the new BEIR and ICRP risk estimates are in line with those calculated by Cardis et al. (2007) for low-dose-rate exposures in radiation workers in the nuclear industry. This is especially important in light of the fact that the primary data source for cancer risk estimates (LSS data) is for acute exposures.

The overall conclusion from BEIR VII (NRC 2006) as regards the use of the LNT in cancer risk estimation for calculating low-dose, low-dose-rate cancer risk estimates is that the difference between the linear and linear-quadratic models is small relative to the error bars (Fig. 2). For solid cancer incidence, the linear-quadratic model did not offer a significant improvement in fit over a linear model, and so the linear model was used. In contrast, for leukemia, the linear-quadratic model was used, as previously, since it fitted the data significantly better than a linear model. Thus, the BEIR VII committee proposed that "current scientific evidence is consistent with the hypothesis that there is a linear, no threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans." Similarly, ICRP (2007) concluded that "the adoption of the LNT model combined with a judged value of DDREF provides a prudent basis for practical purposes of radiological protection (i.e., the management of risks from low-dose radiation exposure in prospective situations)."

The question clearly arises, and does so every time the validity of LNT is discussed, as to whether LNT

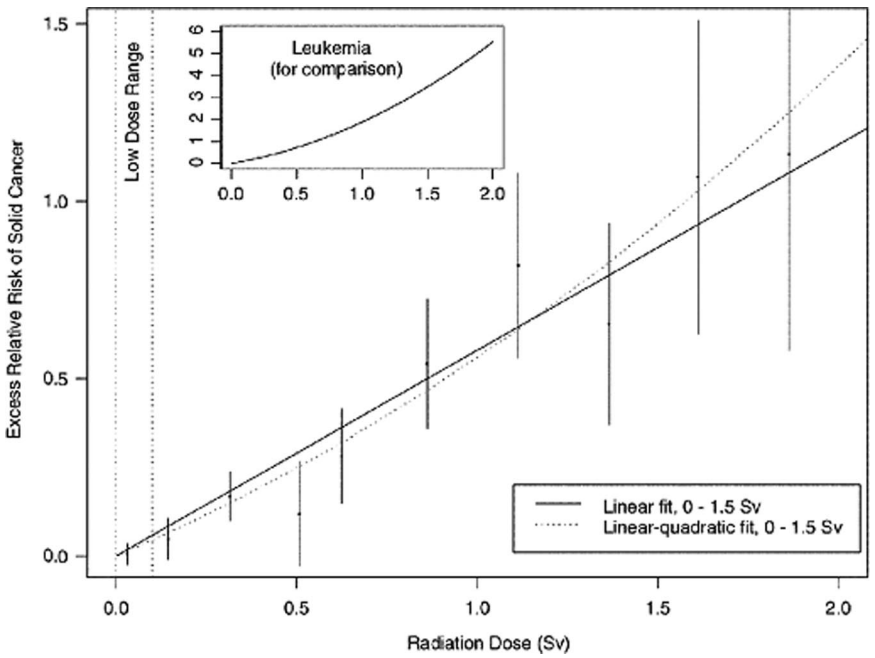

Fig. 2. Excess relative risks of solid cancer for Japanese atomic bomb survivors. Plotted points are estimated excess relative risks of solid cancer incidence (averaged over sex and standardized to represent individuals exposed at age 30 who have attained age 60) for atomic bomb survivors, with doses in each of 10 dose intervals, plotted above the midpoints of the dose intervals. Solid and dotted lines are estimated linear and linear-quadratic models for excess relative risk, estimated from all subjects with doses in the range 0 to 1.5 Sv. The insert shows the fit of a linear-quadratic model for leukemia to illustrate the greater degree of curvature observed for that cancer. (From NRC 2006, with permission.)

underestimates or overestimates the cancer risks at low doses. It is noted here that arguments can be made based on cellular data, largely using in vitro systems, that responses at low doses can be enhanced over a linear extrapolation [e.g., by the induction of genomic instability or bystander responses, reviewed in Morgan and Sowa (2007) and Prise (2006)] or reduced compared to a linear extrapolation [e.g., adaptive and hormetic responses, reviewed in Schwartz (2007) and Johansson (2003)]. However compelling the evidence for nonlinear effects at low doses might be, the context for LNT in radiation cancer risk assessments is for tumor development itself. Since human tumor data are used as the primary data for establishing cancer risk estimates, cellular observations currently serve in a correlative or supportive role. However, it is equally clear that there is a continued need to evaluate a possible relevance for adaptation, low-dose hypersensitivity, bystander effects, hormesis, and genomic instability in radiation carcinogenesis. Such knowledge, together with other mechanistic data, could help in the development of a biologically-based dose-response (BBDR) model for radiation induced tumors in rodents and humans (UNSCEAR 2000).

DDREF: Current estimates

The DDREF generally has been derived from animal in vivo and cellular in vitro studies as a selected value from the range of observed values (about 2 to 10). The ICRP, in ICRP 60 (ICRP 1991), recommended a DDREF of 2 as being protective and scientifically defensible. In addition, the use of an integer was deemed to be practical in terms of radiation protection standards. In its 2007 recommendations, ICRP stated that, in considering the available experimental and epidemiological data, and the broad range of reduction in response for protracted exposures, "the Commission finds no compelling reason to change its 1990 recommendations of a DDREF of 2. However, the Commission emphasizes that this continues to be a broad whole number judgment for the practical purposes of radiological protection which embodies elements of uncertainty." The ICRP used a DDREF of 2 to derive nominal risk coefficients for cancers.

The BEIR VII committee (NRC 2006) took a rather different approach by conducting probabilistic analyses of combined dose-response data using a Bayesian approach. The data sets that were incorporated into the analysis were (1) LSS solid cancer data, (2) cancer and life shortening in animals, and (3) chromosome aberrations in human somatic cells. The median value for DDREF from these analyses was about 1.5 with a range of 1.1 to 2.3. Based on this, the BEIR VII committee selected a DDREF value of 1.5. The BEIR VII committee also recognized the uncertainties associated with their approach.

Heritable risks

A thorough discussion of the current approach for assessing heritable risks and the changes that were made for this latest approach can be found in publications by United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR 2001), BEIR VII (NRC 2006), and ICRP (2007). In summary, there is still no evidence for radiation-induced germ cell mutations in humans although extensive data exist for rodents (acute and chronic exposures). Given the considerable enhancement in knowledge of the molecular underpinnings of genetic disease in humans, the heritable risk process has been extensively revised to include the use of human "spontaneous" data (as opposed to mouse data in previous iterations). Mouse data are, by necessity, still used for radiation-induced mutations. In addition, risk coefficients were calculated up to two generations, as opposed to equilibrium, based on the anticipated level of confidence in the prediction over time. The probability coefficients for heritable disease up to the second generation are 0.2×10^{-2} per Sv for the entire population and 0.1×10^{-2} per Sv for adult workers. The exposures underlying these estimates are continuous, low-dose-rate for two generations. These values are similar to those in previous ICRP, BEIR, and UNSCEAR reports, but it was considered that this similarity was perhaps coincidental given the substantive changes in methodology.

RADIATION RISKS AND CT SCREENING

The 2007 NCRP Annual Meeting focused on applications of radiation in medicine, and full-body CT screening for healthy adults was chosen to illustrate the use of radiation cancer risk estimates in predicting risk for a specific medical procedure.

There is an increasing interest in the use of full-body CT screening of healthy adults as part of a comprehensive health maintenance program. Such an approach has been touted as having potential for early detection of a variety of diseases, including lung cancer, coronary artery disease, and colon cancer. However, the real effectiveness remains unclear (Berland and Berland 2003; Schoeder and Goenen 2007). As noted by Brenner and Elliston (2004), more attention has been paid to the pros and cons of the procedure for disease detection and the potentially high frequency of false positives than has been paid to the parallel concern of the potential radiation risks from the relatively high exposures from each individual CT scan and the accumulated exposure resulting from the proposed annual screen.

Brenner and Elliston (2004) conducted an informative exercise to estimate the radiation-related cancer mortality risks associated with single and repeated full-body CT examinations by using standard radiation risk estimation methods based upon ICRP (1991) and BEIR V (NRC 1990) estimates of organ-dependent lifetime cancer mortality risks (per unit dose). There would be very little difference in the estimates if the cancer mortality risk values provided by ICRP (2007) or BEIR VII (NRC 2006) had been used. Of particular note, the estimates are based on the LNT model as preferred by both ICRP and BEIR VII. The details of the approach are provided in Brenner and Elliston (2004) and only a brief overview is provided here.

The basic approach used for risk estimation was to multiply estimated sex-, age-, and organ-dependent lifetime cancer mortality risks (per unit dose) by estimated organ doses received from full-body CT examination, bearing in mind the very inhomogeneous dose distribution. The estimated organ doses are shown in Table 1 taken from Brenner and Elliston (2004, with permission). It would be equally feasible to have used the detriment-adjusted cancer risks (for cancer mortality and incidence) developed in ICRP (2007). The resulting site-specific estimated cancer risks were summed to yield the overall lifetime cancer mortality risk estimates. The authors refer to Brenner et al. (2001) for additional information on more specific applications.

The excess cancer mortality as a function of age at first annual CT examination is shown in Fig. 3. For this depiction, it is assumed that annual examinations commence at a specified age along the abscissa and continue until age 75 y. For example, the estimated lifetime cancer mortality risks from a single full-body CT examination are about 8×10^{-4} for a 45-y-old adult and about 6×10^{-4} for a 65-y-old adult (with 95% confidence limits of about 3.2). For multiple examinations, the risks are correspondingly higher—30 annual exams for a 45-y-old adult would give an estimated lifetime cancer risk of 1.9% with a confidence limit of about 1.6.

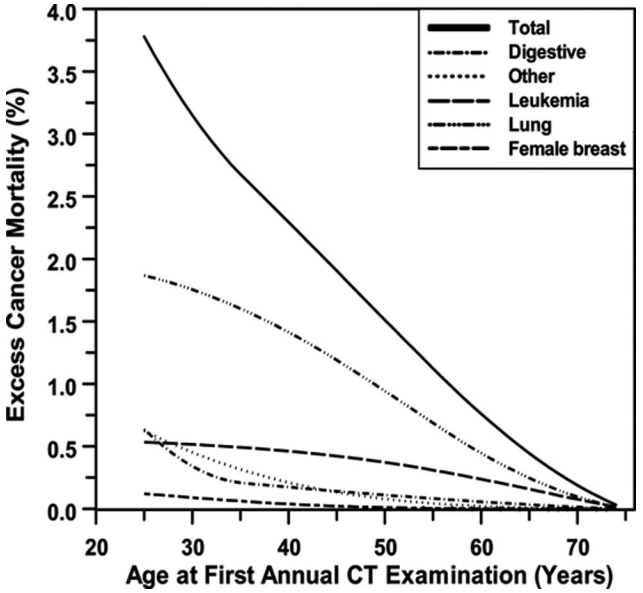

Fig. 3. The excess cancer mortality risks estimated to be associated with radiation from annual full-body CT examinations. Annual examinations are assumed to commence at the specified age and continue until age 75 y. (From Brenner and Elliston 2004, with permission.)

Table 1. Estimated organ doses for a typical full-body CT scan. (From Brenner and Elliston 2004, with permission.)[a]

Organ	Radiation dose (mGy)
Thyroid	24.7
Bone surface	15.7
Esophagus	16.2
Lung	15.5
Stomach	14.4
Liver	14.0
Bladder	13.9
Breast (female)	12.3
Gonads (female)	12.2
Colon	11.6
Red bone marrow	9.9
Skin	7.5
Gonads (male)	2.6

[a] Doses were estimated for a full-body CT examination with a Volume Zoom scanner (Siemens Corporation, Citicorp Center, 153 East 53rd Street, New York, NY 10022-4611) operated at 120 kV and 230 true mAs with a pitch of 1.75. The examination was from C3 vertebra through the symphysis pubis. Dose estimation was performed with the ImPACT CT patient dosimetry calculator (Jones and Shrimpton 1991). Note if a lower amperage setting is used, the doses would be proportionately lower. The total effective dose (weighted average of organ doses) is 13.5 mSv for females and 11.6 mSv for males.

This example serves to highlight the use of the ICRP/BEIR VII cancer estimates and the approaches for calculating risks in the context of a specific medical radiological application. It also highlights the fact that significant risks can be associated with the use of relatively high radiation exposures in annual CT screening, especially under circumstances when it is difficult to establish convincing benefits of the practice.

CONCLUSION

- The prevailing view from BEIR VII and ICRP (2007) is that the low-dose dose-response for solid tumors is linear with no threshold—even when based on cancer incidence;
- The DDREF is chosen as 1.5 by BEIR VII and remains as 2 for ICRP;
- There is a need to continue to evaluate the impact of new cellular data on the radiation carcinogenesis process at low exposure levels;
- There are currently insufficient data to be able to estimate risks for non-cancer endpoints;

- There appears to be no need to change current policy and practice for diagnostic radiological procedures based upon new cancer risk estimates; and
- For emerging radiological applications it is important to include estimations of risk when considering the pros and cons of the application. An annual CT scan is one such potential application.

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