Current Perspectives on the Use of the Linear Non-Threshold (LNT) Model in Radiation Protection

Lynna Tran¹ and Euclid Seeram²*

¹Department of Medical Imaging and Radiation Sciences, Monash University, Clayton, Victoria, Australia
²Medical Imaging and Radiation Sciences, Department of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia

Abstract

The increasing use of radiation in medical imaging and radiation therapy has raised concerns about the biological effects of radiation exposure, such as the stochastic and deterministic effects. Various dose-response models have been developed to address these concerns. One such popular model is the linear non-threshold (LNT). The LNT model developed from studies of catastrophic events to humans including the Hiroshima and Nagasaki atomic bombs, demonstrates the stochastic risks of radiation exposure. Many organisations have adopted the LNT model to form the basis of their radiation protection standards. However, with increasing biological and epidemiological studies have raised doubts on the validity of the model especially at low levels of radiation (<100mSv), whereby no definitive effects have been demonstrated in humans. A review of literature was conducted using Ovid Medline and Scopus databases to evaluate the controversy surrounding the use of the LNT model and the current perspective of radiation protection organisations on its use. The literature debate consists of arguments against the data obtained from epidemiological studies as well as the consequence effects of the LNT model on the public. In response, alternative dose response models that contradict the accepted LNT model, especially at low doses, have been suggested. These include hormesis, hypersensitivity and threshold models. However, there remains a need for continued research on the effects of low doses radiation on specific organs and tissues to further quantify risk estimates. Further knowledge and understanding of these effects will allow for improved radiation protection for patients.

Introduction

Radiation protection consists of a set of developed standards and guidelines used to protect the human population from damaging effects of ionizing radiation. The basis of radiation protection is gained from high levels of radiation exposures analysed from catastrophic events to humans, namely the atomic bombs in Hiroshima and Nagasaki (1945) and nuclear power plant accidents in Chernobyl (1986) and Fukushima (2011) [1,2,3]. The largest emphasis is placed on data provided by the Radiation Effects Research Foundation (RERF) which studies the biological effects on the atomic bomb survivors of Hiroshima and Nagasaki [4]. Biological effects of radiation have been studied extensively and can be divided into two categories deterministic and stochastic effects. Deterministic effects are effects for which the severity of the effect in the exposed individual increases as the radiation dose increases and for which there is a threshold. Examples including skin burns and ulcerations, are present after the threshold dose has been exceeded [1,5]. Stochastic effects on the other hand are effects for which the probability of the effect occurring depends on the dose. The probability of the effect increases as the dose increases and there is no threshold dose. Examples include cancer, leukaemia and genetic effects [6].

Dose response models have been developed from data of high exposure events to determine the stochastic effects of radiation. There is currently little data to support the biological effects of exposure to low doses of radiation (<100mSv), hence the low dose regions of dose response models have been extrapolated from high doses of radiation (>100mSv) during these events [1,7]. Dose response models can be split into two categories, linear dose response models and non-linear dose response models [1]. The linear non-threshold (LNT) model is most widely supported as it demonstrates a response from any amount of radiation and a direct proportionate increase in radiation response with increasing dose [6,7]. A drawback of this model is the increased likelihood of an overestimation of the stochastic effects of radiation [1]. However, as there is little data to support low regions of dose response models, there remains ongoing controversy over the use of the LNT model to govern today’s practice and whether an alternative model is best suited.

Radiation Protection Organizations around the world have produced standards and guidelines on radiation protection, based on the biological effects of ionizing radiation on humans. In doing this, they have analysed many studies, including those produced by RERF, to determine which model best reflects the risk of carcinogenesis at low radiation doses. There is mutual agreement from the majority of organizations including United Nations Scientific Committee on Atomic Radiations (UNSCEAR) and Biological Effects of Ionizing Radiation (BEIR), that the LNT model best demonstrates carcinogenesis risks and hence have continued to base their radiation protection guidelines on the LNT model. However, organizations including the French Academie des Sciences present contrasting opinions and have proposed alternative dose response models [1].

Background Knowledge

Human biological response to ionizing radiation (stochastic and deterministic effects) is dependent on many factors including the radiation source, length of exposure as well as the system irradiated [8]. Some responses of radiation may appear immediately, whilst others may take up to decades to be clinically evident [8].

*Corresponding Author: Lynna Tran, Medical Imaging and Radiation Sciences, Department of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia; E-mail: lynnatran@hotmail.com


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Deterministic Effects

Ionizing radiation has the capability of killing cells once the exposure exceeds a certain limit [9]. Cells can be replaced through cell division, however if the number of cell death is too high, damage to tissues and organs may occur [9]. This damage is known as a deterministic effect. Deterministic effects have a threshold dose, whereby once this threshold dose has been exceeded, effects are observable [8]. As the dose increases, the response rate along with the severity of the effect increases [5,6]. These effects usually present within a few days of exposure, however some can occur much later [9]. For instance, skin erythema usually appears in a few hours to ten days, in contrast to radiation-induced cataract which can present months to years after exposure [9]. Other examples of deterministic effects include tissue damage, organ dysfunction and hair removal, [1,5]. In medical imaging, these effects are commonly experienced in high and lengthy radiation procedures including cardiac interventions and angiography procedures, whereby the effects can be predicted after certain radiation dose levels [1].

Stochastic Effects

Stochastic effects, especially cancer, from radiation of doses below 100mSv are considered the principal health risk [8]. Stochastic effects do not have a threshold dose; hence any amount of radiation has probability of resulting in detrimental effects which are random in nature and independent of dose [10]. The probability of an effect increases with increasing dose, hence a higher dose will result in higher probability of stochastic effects, whereas lower dose results in a lower probability [6]. Radiation can cause mutation or alteration to a single cell, resulting in malignancy after multiple successive cell division [5]. Hereditary effects are also capable of occurring, however from studies of the atomic bomb survivors and radiotherapy patients, these effects have yet to be demonstrated [8]. Stochastic effects occur later than deterministic effects and are usually not observable until many years after exposure [5]. Radiation protection organisations have used dose response models to put in place radiation limits to minimise the probability of stochastic effects occurring [8].

Dose Response Models

Dose response models demonstrate the magnitude of the ionizing radiation response as a function of the exposed dose. These models have been derived from epidemiological studies of human exposures to large (>100mSv) amounts of radiation. From the RERF data based on Japanese atomic bomb survivors, an increase in cancer incidence has been derived from epidemiological studies of human exposures to large (>100mSv) amounts of radiation [12,17]. This data, demonstrates results from larger doses of radiation (>100mSv) extrapolated to low doses. However, this is unable to accurately demonstrate risks from radiological procedures, whereby doses are of a much smaller magnitude. As it is unethical to expose patients unnecessarily for research purposes, there is little data that can provide evidence of the effects of radiation to humans at low doses.

1. Absence of human response to radiation at low doses [12,17,18]. The basis of the LNT model is data from Life Span Study (LSS) of the atomic bomb survivors [12,17]. This data, demonstrates results from larger doses of radiation (>100mSv) extrapolated to low doses. However, this is unable to accurately demonstrate risks from radiological procedures, whereby doses are of a much smaller magnitude. As it is unethical to expose patients unnecessarily for research purposes, there is little data that can provide evidence of the effects of radiation to humans at low doses.

2. Debate against the use of data from LSS study [12]. Aleu (2009) and UNSCEAR (2010) argues that the use of this data is only applicable to the exposed group of individuals, as this is a unique dataset and these non-workers and the public are not exposed to this amount of radiation daily [17,19]. Those who were within 10km of the isocenter of either the Hiroshima or Nagasaki bombs were exposed to 200mSv of radiation, in comparison to 1mSv/year suggested for the public [4]. Data from the LSS study also only considers the acute exposure from the atomic bombs and fails to take into consideration exposure due to fallout and induced radioactivity [12].

3. Raised fear of radiation, radiophobia, in the public [7,12,13,15,16,20,21]. As the model represents risk associated with any exposure to radiation, this causes unnecessary concern and alarm in the public population [13,15,20]. Radiophobia can have drastic effects on the general public, especially for those who refuse medical examinations and surrender the opportunity of clinical benefits [16]. This is also of great concern especially for populations whom live in regions exposed to naturally high amounts of background radiation levels including Ramsar (Iran), Yangjiang (China), Scandinavia, France and Russia [7,22]. High natural background radiation is considered to be greater than 20mSv a year.

4. Waste of economic resources [7,12,15,20]. Economic resources are used to uphold the compliance of radiation protection standards in various medical imaging departments. The LNT model raises concerns over the damaging effects of radiation at low doses, hence an increase in compliance costs is required to uphold regulations to ensure that recommended safety limits are not exceeded [12].

The Debate

There has been extensive controversy over the use of the LNT model, especially at low doses, in creating safety regulations for use in radiation protection [12,13,15,16]. Due to the damaging effects of radiation at high doses, there is belief that based on biological studies there is damage no matter how small or unobservable at low doses [12]. A range of reasons have been raised against the use of the LNT model including:


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5. No radiation induced genetic or hereditary effects have been proven in humans [10]. Based on the study of atomic bomb survivors of more than fifty years, no genetic or hereditary effects have been evident in the exposed population [12]. Due to raised fears of radiation induced genetic effects, more than 100,000 pregnancies were terminated in Western Europe following the Chernobyl accident [15,16,20].

6. Contradictory shape of dose response curves at low doses based on biological and epidemiological studies [17]. Many different studies have demonstrated differing dose response curves at low doses including, thresholds, linear quadratic relationships and hormesis response.

7. Factors affecting DNA damage [23]. By splitting the dose delivered into fractions, the body tissues are capable of repairing prior to the next exposure. Making use of a lower dose rate will also reduce the DNA damage.

The LNT model: Current Perspectives of Radiation Protection Organizations

Due to controversy of the LNT model, radiation protection organizations have based their radiation protection standards on varying views. These organizations have individually reviewed many epidemiological and biological studies to base their conclusions on the use of the LNT model and which dose response model is preferred to best protect humans. The 2007 Recommendations of the International Commission on Radiological Protection (ICRP) and the National Academies of Science and National Research Councils (NAS/NRC) Committee on the Biological Effects of Ionizing Radiation (BEIR) VII Report have been used extensively to support the conclusions of many organizations.

The International Commission on Radiological Protection (ICRP) has reviewed and analysed data from a variety of data sets including studies of atomic bomb survivors, medical radiation, occupational and environmental exposures [10]. As stochastic effects are based on probability, it is difficult to distinguish between safe and dangerous radiation dose levels. The increase in support of tumorigenesis from biological studies and understanding of the effects of radiation on DNA, including double strand breaks and cellular division, have strengthened support for the LNT model [10]. ICRP recognises that, although there are studies that have differing conclusions to that of the LNT model, the majority of the weight of evidence is in support of the increasing probability of cancer or genetic mutations with increasing dose [10]. However, despite the lack of definitive data of radiation damage at low doses, ICRP has recommended that use of the LNT model in conjunction with a dose and dose rate effective factor (DDREF) is a conservative method and should be used as the basis of radiation protection standards [10].

The DDREF was first introduced in 1980 by the National Council of Radiation Protection (NCRP). The DDREF is used to determine risk estimates at low doses and low dose rates by extrapolation from high doses and high dose rates [24,25]. The DDREF takes into consideration biological repair post radiation exposure to provide a more accurate risk estimate [19]. Once again, there is varying notions of the value of DDREF that should be used with linear models. The ICRP (2007) has recommended a DDREF of 1.5 and UNSCEAR (2010) suggested a DDREF of no more than 3, further reinforcing these varying notions.
required in the field and that future studies must be considered when determining radiation risk models.

Both the Cancer Nuclear Safety Commission (CNSC) and Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) have developed their radiation protection standards based on the ICRP's 2007 recommendations [29,30]. To monitor the use of nuclear energy and substances to protect Canadians and the environment from radiation exposure, the CNSC consider the findings of both the ICRP and the BEIR VII Report [29]. In their recommendations, the CNSC conclude that the LNT model is prudent and concurrent with international standards. ARPANSA develops guidelines to protect the Australian public, medical imaging workers, nuclear workers and the environment from the damaging effects of radiation. ARPANSA recognises that there are varying dose response models at low doses, however the LNT model is accepted as it is conservative and prudent, despite the epidemiological studies against it [30]. The CNSC and ARPANSA share similar recommendations for the regulatory limit, with both committees suggesting 1mSv a year for the general public and 100mSv over a five-year period for radiation workers, with a maximum limit of 50mSv per year [29,30]. Both committees state that despite the uncertainty of the dose response curve, the dose should always be kept “as low as reasonably achievable” (ALARA) [29,30].

In contrast, the French Academie des Sciences (2005) share opposing views to all other organisations stated above. They believe that the LNT model is not credible to assess the risks of low levels of radiation (<100mSv) as the model is not based on valid scientific evidence [23]. The organisation presents a view that the cell cycle changes with time and location and so the cellular mortality and cellular repair rates will vary dependent on the stage of the cell cycle and the location of the irradiated cell. This viewpoint is further supported by the lack of epidemiologic studies yet to show a significant increase in carcinogenesis at low doses in humans and animals [23]. Data from many animal studies indicate the presence of a threshold and demonstrate no increase in cancer effects at doses below this threshold [23]. Hormesis has also been concluded in approximately 40% of studies, further raising concerns on the overestimation of the LNT model. The French Academie des Sciences has provided two reasons for the lack of cancer incidence at low levels of radiation: (1) The cancer incidence effect is too small to be observed, (2) There is no carcinogenesis at low doses and a threshold is present. Based on analysis of numerous studies, the French Academie des Sciences strongly support the existence of a threshold, however the threshold level is unable to be quantified from current available data [23]. A level between 10-50mGy has been suggested, but it is noted that this level will vary depending on the cell type and person’s age.

Alternative Dose Response Models

As there is much debate over the use of the LNT model, alternative models have been suggested to represent stochastic risks at low doses. These models have been developed from epidemiological studies and have proven to be valid under the specific parameters used in these studies including radiation source, dose and dose rates. From these studies, three models represented in Figure 1 have been suggested [1]:
1. Hormesis model (green) - at low levels of radiation, beneficial effects are demonstrated.

2. Hypersensitivity model (orange) - at low levels of radiation, effects are higher than those represented by the LNT model.

3. Threshold model (purple) - below a certain threshold, no effects of radiation are demonstrated.

The hormesis model, also known as the adaptive model, includes a threshold, whereby at doses below this threshold, beneficial and protective effects are observed [1,4,6,8,11,13,16,31,32]. At doses above this threshold, the hormesis model remains linear with the risk of carcinogenesis increasing linearly with dose. Essentially, an exposure to low level of radiation will prime and prepare the DNA repair systems for when it encounters a second exposure, it can effectively respond [13,33]. Various studies of animals exposed to low levels of radiation have resulted in longer mortality rates than those of the control study [6]. These results have been considered to be due to the low radiation stimulating and elevating hormonal and immune responses for protection. A study conducted by Sykes et al. (2006) tested the inversion of chromosomes in the spleen by exposing mice to x-rays of approximately 0.01Gy followed four hours later by an exposure of 1Gy. This study could demonstrate that mice that had received two exposures experienced fewer chromosomal inversions as opposed to those in the control group who had one single radiation exposure of 1Gy [34]. The initial increase in mutation frequency is accounted to the bystander effect, whereby at extremely low levels of radiation not all cells will experience DNA damage [34]. Figure 2 demonstrates these said hormesis effects in the aforementioned study.

This model is further supported by a study conducted on 400,000 nuclear workers from 15 different countries [22,24]. The study analysed the deaths of the workers to determine whether they were as a result of cancer or alternatively due to another cause. The study concluded in a decrease in deaths overall in comparison to the control study as well as a decrease in cancer related deaths among the nuclear workers [17,22,24]. Despite these studies, the hormesis model is subject to high discrepancy dependent on factors including the dose, dose rate, time between doses and genetic variation of cells [13].

The hypersensitivity model at low doses, demonstrates greater risk of carcinogenesis in comparison to the LNT model. As the dose increases, the hypersensitivity model is comparable to the LNT model (Figure 1). This model is mediated by the bystander effect, in which at low doses, radiation will result in the induction of DNA repair responses in non-irradiated cells bordering the irradiated cells [13,33]. As a result, there is an increase in the number of affected cells. Bystander effects are predominantly observed during cellular reproduction of irradiated and non-irradiated cells and relocation of irradiated cells into a medium of non-irradiated cells alone [13,32,35]. Various studies have demonstrated a rise in the prevalence of mutations, cell death, DNA repair and damage as a consequence of these bystander effects [13,35]. The hypersensitivity model is strongly supported by a study produced by Ojima, Ban and Kai (2008) in which the number of double strand breaks (DSBs) caused by the irradiation of human fibroblasts were analyzed [36]. Quantity of DSBs was determined from the number of phosphorylation of the ataxia telangiectasia mutated (ATM) foci, which develops as the cell’s response to a DSB. A hypersensitivity dose response model was concluded, for doses ranging from 1.2 – 5mGy (Figure 3). As the radiation dose increased up to 200mGy, the steepness of the dose response model decreased. The hypersensitivity model differs from the LNT model, whereby the stochastic risks at low doses is greater than those suggested by the LNT model.

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Figure 2: Hormesis dose response curve of mice exposed to a priming dose (0.01Gy) of radiation followed by a larger dose (1Gy). The LNT model is also demonstrated for comparison [34].

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Another alternative model that has been suggested is the threshold model, in which dose exposures below a specified threshold level are considered to be harmless \[1,16,37\]. Above the threshold, the stochastic effects continue to increase linearly with dose. This threshold phenomenon is supported by a consensus that exposures to a radiation dose less than 0.05Gy will produce no harmful effects on a foetus during any period of the gestation term. This study analysed for mutational, physical and mental effects of a range of radiation exposures to foetuses during a range of gestation periods (Figure 4) \[38\]. As shown in Figure 4, no cancer related effects were demonstrated below doses of 0.05Gy, further prompting the existence of a threshold at 0.05Gy. The threshold model however is subject to a wealth of controversy as the threshold level will vary dependent on the individual exposed, the dose and dose rate as well as the period of gestation for foetuses \[38\]. The threshold model is highly endorsed by the French Academie des Sciences (2005) who strongly believe the existence of a threshold at low levels of radiation.

Figure 3: Hypersensitivity dose response model of phosphorylation ATM foci in irradiated human fibroblast cells \[36\].

Figure 4: Possible effects of radiation of foetus’ exposure during different stages of the gestation period. Below doses of 0.05Gy, no cancer health effects are detected, providing further support for a threshold dose response model \[38\].
Limitations and Future Direction

As the LNT model is predominantly based on unplanned disastrous events to human populations, the exact quantity of the radiation exposure experienced by individuals is unable to be definitively determined. Extrapolation from these results to low doses is unfeasible as the doses exposed in these events are much higher than exposures used in medical imaging [4,17,19]. General radiography and mammography examinations result in exposures of less than 1mSv, whilst examinations such as computer tomography and fluoroscopy can expose patients to doses of 5–15mSv [39]. These warrants further research of the effects of low radiation dose on humans, especially in the range used in medical imaging. A drawback however, would be the unethical nature of unnecessarily exposing asymptomatic populations for experimental purposes whereby beneficial results do not outweigh the resultant harm. A suggestive method is to monitor the populations that live in regions of high natural background radiation and those that are exposed to radiation regularly for diagnostic or treatment purposes.

Human epidemiology studies have yet to provide appropriate risk estimates that can be used for patients routinely exposed to radiation for treatment purposes such as radiotherapy [9]. Dose-response models vary dependent on many factors including dose, dose rates, method of dose calculation as well as the radiation source [40]. Further understanding of the molecular and cellular effects of radiation as well as further investigation into the carcinogenesis effects of different organs and tissues is highly recommended [2,4]. The effects of radiation on the interaction between different cell types should also be investigated, as the human body is made up of a variety of cells [33].

As radiation protection organisations present different perspectives on use of the LNT model, an international meeting is proposed, in which the risks and effects of radiation on human health can be discussed [3,18]. In doing this, scientific evidence and common ideas can be accepted, meanwhile gaps in research can be identified for future investigations [3,18].

Conclusion

The use of radiation for diagnostic and treatment purposes of the human population has thoroughly increased, and this has resulted in a need for a greater understanding of the effects of radiation especially at the low doses used in medical imaging. The LNT model, in which stochastic risk increases linearly with dose, has been the gold standard of practice, however its premise for use is based on evidence gained from catastrophic events to humans namely the Hiroshima and Nagasaki atomic bombs in Japan in 1945. This is highly controversial as the doses exposed during these events are much larger than those experienced in medical imaging examinations. The lack of genetic or hereditary effects as well as the absence of data on human response to radiation doses less than 100mSv, is believed to create unnecessary fear of radiation in addition to being a waste of economic resources to uphold current radiation safety regulations. The inconclusive effects of radiation at low doses have resulted in varying opinions on the validity of the LNT model as well as suggestions of alternative models.

Although they do not rule out the possibility of an alternative model, the majority of the radiation protection organisations incorporate the LNT model when forming the basis of their codes of practice. The ICRP, BEIR VII and UNSCEAR recommend the use of the LNT model in conjunction with a DDREF value to provide a more accurate risk estimate. Smaller organisations such as the CNSC and ARPANA rely on recommendations of the ICRP to form their codes of practice. As the majority of the evidence available is in favour of the LNT model, these organisations believe the LNT model to be conservative, consistent and convenient for radiation protection. However, the French Academie des Sciences believes an alternative threshold model is best to represent low doses with a threshold existing between 10-50mGy.

Three alternative models suggested to represent radiation risk are the hormesis model, hypersensitivity model and the threshold model, all of which contradict the LNT model at low doses. There is evidence of epidemiological studies which support each model however, these studies all vary based on many factors including dose, dose rate, time between exposures and radiation source. Organisations have recommended for continued research on the effects of low dose radiation. This can be achieved through monitoring of populations living in regions of high natural background radiation or those who are routinely are exposed to radiation for diagnosis and treatment. Further understanding of the effects of radiation on different tissues and organs will allow for more accurate risk estimates and ensure the safety of those receiving medical imaging examinations and radiation therapy treatment.

Competing Interests

The authors declare that no competing interests exist.

References


