The British Journal of Radiology, 85 (2012), e1166–e1173

INVITED REVIEW ARTICLE

Radiation-induced cancer: a modern view

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ABSTRACT. Diagnostic medical radiation has been the most rapidly increasing component of population background radiation exposure in Western countries over the past decade. This trend is set to increase as CT scanning is readily available with burgeoning use in everyday clinical practice. Consequently, the issue of cancer induction from the doses received during diagnostic medical exposures is highly relevant. In this review we explain current understanding of potential cancer induction at low doses of sparsely ionising radiation. For cancers that may be induced at low doses, a mechanistic description of radiation-induced cancer is discussed, which, in combination with extrapolation of data based on population cohort studies, provides the basis of the currently accepted linear no-threshold model. We explore the assumptions made in deriving risk estimates, the controversies surrounding the linear no-threshold model and the potential future challenges facing clinicians and policy-makers with regards to diagnostic medical radiation and cancer risk, most notably the uncertainties regarding deriving risk estimates from epidemiological data at low doses.

Received 12 February 2012
Revised 24 July 2012
Accepted 6 August 2012

DOI: 10.1259/bjr/25026140

This review summarises current thinking on how to estimate the cancer risk due to [low linear energy transfer (LET)] ionising radiation doses in the range relevant to diagnostics, from <1 mGy to ~50 mGy. Data derived from epidemiological studies at higher doses (up to ~1.5 Gy) usually involve a number of complex additional effects not directly relevant to the low-dose estimates.

The fact that ionising radiation causes cancer in humans has been known for over a century. In 1902, the first radiation-induced cancer had been reported in an area of ulcerated skin. By 1911, there were even reports of leukaemia arising in radiation workers [1]. Our understanding of radiation carcinogenesis has vastly progressed since the Second World War because of animal models [2], and also because of the important epidemiological evidence arising from the Life Span Study of the Japanese Atomic Bomb survivor cohort [3]. This cohort is absolutely crucial to our understanding and estimation of cancer risk from ionising radiation. Its usefulness is the result of: the large size of the studied population (approximately 100 000 survivors); the long length of follow-up (over 60 years); the breadth of the population exposed (including males and females of all age groups); the fact that population selection was not in any way based on cancer status; the variation of doses received, ranging from the low doses relevant to diagnostic medical radiation to much larger, even lethal, doses; and the fact that individuals received a whole-body exposure rather than targeted exposures to individual organs, so that risks for most solid cancers/leukaemias can be estimated.

There is strong epidemiological evidence that the relationship between radiation exposure and solid cancer induction is approximately linear for ''intermediate'' doses from approximately 0.15 Gy to approximately 1.5 Gy (*i.e.* a range of approximately 1 log). However, the large numbers of exposed individuals at low doses required to induce a statistically significant number of cancers has precluded definitive epidemiological study of the shape of the dose–response curve at levels most relevant to medical diagnostics.

The best that can be done based on our current evidence is to extrapolate down the linear curve at intermediate doses to those levels encountered in diagnostic radiology, *i.e.* <0.1 Gy. Unfortunately, the lack of reliable evidence at low doses has led to considerable controversy about the shape of the dose–response curve at low doses (Figure 1).

The linear no-threshold model

In this section we emphasise human cancer data, rather than surrogate end points. The linear no-threshold (LNT) model assumes a curvature at moderate doses, but linearity at low doses or low dose rates. However, for the low doses and dose rates relevant to diagnostic radiology, the curve can be assumed to be linear (Figure 1, curve c). It is consistent with the data for solid tumours at doses <1.5 Gy in the Life Span Study.

The central assumption made with the LNT model is that the rate-limiting event in low-dose radiation

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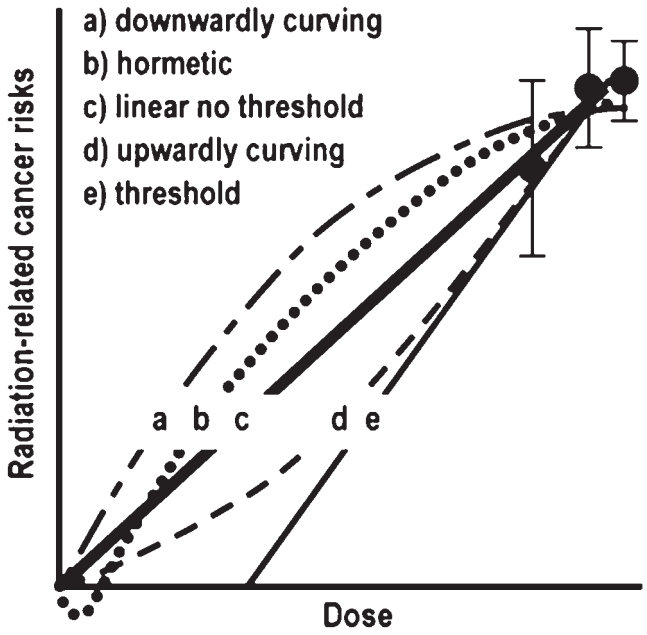

Figure 1. Schematic representation of different possible extrapolations of measured risks to lower doses. The data points schematically indicate results at the lowest doses for which convincing post-natal, epidemiological cancer dose–response data are available. The curves are extrapolations down to still lower doses, based on *in utero* data, surrogate *in vivo* human end point data, mechanistic biophysical models, animal experiments, *in vitro* experiments and/or computer simulations. Adapted from Brenner et al [35].

carcinogenesis is due to ''one-track action'', *e.g.* one or more DNA double strand breaks (DSBs) caused by a single electron track. Dose is directly proportional to track number. Cancer risk owing to one-track action is therefore proportional to dose, with any dose, no matter how small, able to induce cancer (although extremely unlikely to do so). The main rationale for the one-track action assumption is as follows:

- Epidemiological evidence from the studies of *in utero* radiation exposure has shown that a dose of 6 mGy is associated with an increase in cancer risk [4].
- A subsequent comprehensive review in 1997 by Doll and Wakeford [5] concluded that fetal irradiation *in utero* with diagnostic X-rays giving an organ dose of 10 mGy produced a consequent increase in the risk of childhood cancer.
- It is known that, at the dose of 10 mGy, one cell nucleus is typically irradiated with ~10 electron tracks or fewer, depending on the details of the cell and the low-LET radiation [6]. The tracks are then typically far apart in space (>1 μm) and in time (>1 ms). On biophysical grounds it is difficult (although, as discussed later, not impossible) to conceive how two independent electron tracks that are remote in space and time can cooperate (synergistically or agonistically) to increase or decrease the cancer risk. Thus it can be concluded that in all likelihood the key rate-limiting event at 10 mGy is due to one-track action.
- If one-track action can cause cancer, then it follows that reducing the radiation dose by a factor of 10 will simply reduce the number of electron tracks by a factor of 10, and therefore reduce the probability of cancer initiation by the same factor.
- A linear model, with no threshold dose below which radiation is safe, is therefore the most appropriate model in the absence of strong evidence to the contrary.

Modifications from linearity: leukaemia incidence and dose and dose rate effectiveness factor

The LNT has been modified slightly in two respects: data from the Life Span Study for the incidence at intermediate doses of leukaemias (other than chronic lymphocytic leukaemia, which seems to be non-radiogenic [7]) correlate well with a linear-quadratic curve [8], similar to that shown in Figure 1, curve d; and the concept of dose fractionation has led to the introduction of a dose and dose rate effectiveness factor (DDREF) for risk decrease when these quantities are small, which has been suggested as 1.5 or 2 [9]. The value of 1.5 is from the Biological Effects of Ionizing Radiation (BEIR) VII report [9], which used a Bayesian approach with priors based on animal experiments to analyse the low-dose portion of the atomic bomb Life Span Study.

One basis of a DDREF is the relative protection from radiation damage observed for many end points if the same dose is delivered over an extended time, as opposed to the single acute doses seen in the Life Span Study. It is plausible that, by administering a given dose at a lower dose rate or by splitting it into many fractions, the biological system has more time to repair the damage, so that the total damage induced will be less than that expected for the single dose [8]. However, studies on radiogenic cancers in workers occupationally exposed to low dose-rate radiation have concluded that lower DDREFs, *e.g.* 1.2, seem reasonable, thus somewhat strengthening the epidemiological case for LNT estimates [10].

Radiation risks are reviewed by international and national organisations. The radiation protection community has adopted the LNT model for radiation risk at low doses. The breadth of evidence has been comprehensively evaluated and the LNT model ratified by the BEIR VII report [9], the International Commission on Radiological Protection (ICRP) [11] and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) [12]. The LNT model now forms the basis of modern radiation protection policy, although there is controversy about its continued use, most notably from the French Academy of Sciences report [13].

Immune response relevant to the linear no-threshold model (immunosurveillence)

It has been claimed that the immune system is capable of faithfully removing pre-malignant and early tumour cells, allowing the possibility of a practical threshold such as curve e in Figure 1. A criticism of this viewpoint is the presence of large numbers of pre-malignant cells present *in vivo* [14], which would be removed by immune surveillance mechanisms, were they clinically significant. Laboratory experiments have for over three decades demonstrated the well-studied phenomenon of ''dilutional escape'' of small numbers of tumour cells

from host defences [15, 16], highlighting that immune surveillance mechanisms are less effective at dealing with small numbers of tumour cells, even when large numbers are successfully eliminated. Moreover, some cancers are completely refractory to immune treatment altogether. Therefore, in contrast to the views expressed by the French Academy report [13], a practical threshold below which the immune system eliminates cancer risk entirely does not seem likely.

Animal and *in vitro* experiments relevant to the linear no-threshold model

It has often been stated that at low doses the linear relationship suggested by the LNT model is incorrect, and that in fact the radiosensitivity of a tissue to oncogenic transformation increases or decreases with dose. Possible mechanisms for non-linearity include: DNA damage prevention and repair mechanisms; senescence; bystander effects; and genomic instability. A hormetic response (Figure 1, curve b) is suggested by some investigators to occur owing to adaptive responses to radiation. This would have the effect of lowering the dose–response curve for excess relative risk (ERR) in the low-dose region to a level below zero; in other words, suggesting that low-LET radiation may actually have beneficial effects in terms of reducing cancer [17]. Many of the arguments against LNT extrapolations do not clearly distinguish between evidence for non-linearities at low doses and evidence that the non-linearity means that LNT overestimates (rather than underestimates) cancer risks at low doses. Many of the arguments emphasise animal or *in vitro* experiments, whose greater precision at low doses compared with epidemiological data is offset by the formidable difficulties of deciding whether the end points analysed are appropriate surrogates for *in vivo* human cancer [18]. For example, excess cell killing *in vitro* at low doses might suggest that there is also excess oncogenic transformation at low doses, might to the contrary suggest that at low doses oncongenically transformed cells are preferentially killed, or might be irrelevant to human cancer. However, evidence for low-dose non-linearity does substantially weaken the one-track action assumption discussed above. We now survey a few of the experiments that have been analysed.

DNA damage prevention

It is a well-observed phenomenon *in vitro* and *in vivo* that cells exposed to ionising radiation and, hence, reactive oxygen species (ROS), exhibit upregulation of key antioxidants for several weeks. This involves an increase in reduced glutathione and superoxide dismutase, which is maximal approximately 4 h after exposure but lasts for several weeks [17]. It seems logical that all cells should have such robust mechanisms to combat oxidative stress, as the very process of oxidative phosphorylation makes necessary the successful removal of potentially carcinogenic ROS. What is unclear and extremely difficult to conclude is the relative importance of this mechanism in radiation-exposed cells in altering the shape of the low-dose curve.

DNA repair

There are high-fidelity mechanisms of error-free DNA repair in mammalian cells that have been present in unicellular organisms for 600 million years. *Deinococcus radiodurans* bacteria (as suggested by the species name) can tolerate radiation doses of 7 kGy, roughly 1000 times the dose lethal to humans [19]. However, as stated by Tubiana et al [20], multicellular organisms are far more sensitive to radiation exposure. Nevertheless, the authors cite that, at low doses and dose rates, DNA repair is error free, with progressively more errors as dose and dose rate increases [20–24]. This has been extensively studied using human fibroblasts [21, 25].

Apoptosis and senescence

A further mechanism of radioprotection is radiation-induced apoptosis. This is a valuable response of the host response armoury to cellular damage by ionising radiation and other causes of ROS. Multicellular organisms normally eliminate radiation-damaged cells effectively through apoptosis [26–29]. The concept of physiological cell death was developed by Kerr et al [26] some 40 years ago with the publication of a seminal paper on apoptosis. Indeed, most human cancers are associated with defects in apoptosis, such that recent research has highlighted the use of compounds that induce apoptosis as chemoprevention against cancers [30]. Apoptosis mechanisms may not be activated at doses of radiation <5 mGy [30], and may not be effective at doses >200 mGy [20]. However, for the ranges of dose commonly encountered in diagnostic radiology, particularly with regard to CT examinations (5–50 mGy), apoptosis may be a relevant intrinsic mechanism for reducing the risk of cancer.

Senescence is an alternative cellular pathway for eliminating genetically defective cells, the benefit being that functional advantages are retained prior to cell death [31–33]. Whether this is an important mechanism for eliminating radiation-damaged cells is not yet known *in vivo*.

Importance of intercellular interactions to the dose–response curve

Intercellular interactions are ubiquitous in biology. They are potentially relevant to the LNT model. For example, we argued above that the damage from one electron track is unlikely to interact, synergistically or agonistically, with damage from another electron track further away than 1 μm. We concluded that at 10 mGy one-track action dominates, and used this result to argue for the LNT model. But suppose, to the contrary, that tracks in two different cells can produce damages which in effect interact via intercellular interactions. Then the key dose below which we can count on LNT behaviour is drastically lower than 10 mGy and this particular argument in favour of LNT becomes irrelevant—there could be deviations in either direction (Figure 1, curve a, *vs* Figure 1, curves b, d or e) at the doses of interest. Much has been studied in radiobiology about one particular kind of intercellular interaction: ''bystander effects'' in cells remote from radiation-damaged cells. These cells are

not directly affected by traversing electron tracks from ionising radiation sources, but still display remote effects.

Xu et al [34] showed that low doses of radiation, in the range commonly received as a result of medical diagnostic procedures (0.25–10 mGy), stimulate the expression of interleukin 2 (IL-2) receptors on the surface of peripheral blood lymphocytes taken from normal human donors. They irradiated human lymphocytes with a dose of 10 mGy, and calculated the percentage of IL-2 surface receptors 24 h later. There was a statistically significant percentage increase in IL-2 receptors compared with a control group (17.8 ± 3.3 compared with 7.7 ± 4.1; $p<0.01$).

Xu et al [34] concluded that their ''data demonstrate a possible defence mechanism against environmental stress by which a radiation-exposed cell can use an indirect signalling mechanism to communicate with and influence the biological processes in an unexposed cell.''

This suggests that there almost certainly are bystander effects in operation involving intercellular signalling *in vitro*; what cannot be concluded, however, is that these bystander effects predominate over the essential stochastic ''one-track action'' caused by a single electron track *in vivo*, and therefore that they would modulate the LNT curve to any significant degree.

Bystander cell-killing effects are generally considered to result in oncogenic damage to remote cells from the radiation track by the generation of gap-junction or cytokine-mediated cellular toxicity and ROS. At low doses the bystander effect is observed by the activation of large numbers of cells, the response of which becomes saturated as the dose increases [35]. However, just as bystander effects may increase the cancer risk at low doses compared with an LNT estimate by causing a downwardly curving dose–response relationship such as Figure 1, curve a, they may also be negative and serve to reduce the risk of cancer at low doses.

When medium from irradiated mammary carcinoma cells was transferred to non-irradiated cells 120 min after a dose of 2 Gy, soluble transforming growth factor that was released induced secondary activation of epidermal growth factor receptor, mitogen-activated protein kinase and c-*jun* N-terminal kinase, which resulted in an increase in cell survival [36].

For such reasons the BEIR VII report from the US National Research Council states that ''until molecular mechanisms of the bystander effect are elucidated, especially as related to an intact organism, and until reproducible bystander effects are observed for low-LET radiation in the dose range of 1–5 mGy where an average of about one electron track traverses the nucleus, a bystander effect of low-dose, low-LET radiation that might result in a dose–response curving either upwards or downwards should not be assumed'' [9].

Low-dose hypersensitivity and induced radioresistance

Some investigators have noted a pronounced hypersensitivity to low radiation doses <200 mGy, producing survival in cell lines which is 85–90% less than would be predicted by simple extrapolation of linear models [36]. Joiner et al [37] suggested that low-dose hyper-radiosensitivity (HRS) and induced radioresistance (IRR) may be two aspects of the same phenomenon, as adaptive responses may be triggered by a small conditioning dose, which is only effective above a certain threshold dose. Hence, low doses cause relatively more cancer initiation or HRS, and higher doses may protect against subsequent larger doses given after the initial dose (adaptive response or IRR). Both the adaptive response and HRS/IRR have been well documented in studies with yeast, bacteria, protozoa, algae, higher plant cells, insect cells, mammalian and human cells *in vitro*, and in studies on animal models *in vivo*.

However, the relevance of this to human radiation protection generally, and the shape of the low-dose LNT curve specifically, is questionable. Some authorities have suggested that HRS in other species may relate to the amount of time that a cell cycles in radiosensitive G2 phase [38]. As radiosensitive human stem cells, which are the prime targets in cancer induction, tend to spend the majority of their cycle in G0, the significance of HRS *in vivo* is debatable [8].

Exposure of cells or animals to radiation at a low dose and dose rate induces mechanisms that protect against the detrimental effects of other events or agents, including radiation. This is a well-documented phenomenon in *in vitro* and *in vivo* studies for carcinogenesis [39], cellular inactivation [40], mutation induction [41], chromosome aberration formation [42] and *in vitro* oncogenic transformation [43].

What is more controversial is whether any subsequent radioresponsiveness is eliminated from a priming dose, and moreover whether there is a relevant long-lasting effect of any putative IRR. Current evidence suggests that the IRR is transitory, lasting up to 48 h, and therefore of limited relevance to patients or radiation workers who are likely to receive protracted, but low-dose, radiation exposures [34].

Furthermore, one study using human peripheral blood lymphocytes exposed to an initial priming dose followed by a subsequent larger dose concluded that IRR may be age related [44]. However, the sample size was small, precluding definitive conclusions to be drawn from it.

The question of adaptive responses has been documented *in vivo* and *in vitro* and has been thoroughly reviewed by the ICRP and UNSCEAR, who observed that the protective effect of the conditioning dose appears to last only for a few hours and the ability to induce an adaptive response differs between individuals, with some failing to respond at all. It can therefore be concluded that decisions regarding the shape of the dose–response curve and potential variations from the linear response at low doses should not at present be done on the basis of any potential adaptive response to radiation.

Genomic instability

Some investigators have noted a phenomenon of genomic instability, in which cell progeny are affected by DNA damage in the parent cell. This may be related to the effects of chromosomal aberrations [45–48]. Available evidence from human tissue experiments with low-dose exposures suggests that this instability effect mainly relates to α-radiation [9]. Furthermore, an

experiment by Boulton et al [48] in 2001 showed no correlation between the inheritance patterns of radiation-induced genomic instability and radiation-induced leukaemia/lymphoma in mice models, concluding that susceptibility to radiation-induced leukaemia/lymphoma is genetically separable from sensitivity to radiation-induced genomic instability. Once again, alterations to the dose–response relationship based on genomic instability considerations would be unwise in the absence of more convincing data to the contrary.

Mechanistic surrogates for carcinogenesis: γ-H2AX repair foci

A central assumption made with most *in vitro* studies is that a DSB is a reliable surrogate for the mechanism by which ionising radiation causes cancer. The problem arises in reliably inducing a DSB *in vitro* with the low doses which are sparsely ionising in diagnostic radiation. Consequently, great interest has arisen in the use of a phosphorylated histone (γ-H2AX) as a surrogate marker for a DSB [24]. In some papers this surrogate has been found to correlate one-to-one with a DSB, and be reliably detectable with immunofluorescence. Studies have been performed *in vivo* after individuals have been subjected to CT examinations, to measure the numbers of γ-H2AX repair foci by immunofluorescence. This may eventually prove to be a very useful tool for quantifying actual DNA damage *in vivo* at the doses routinely received in diagnostic radiation exposures [49]. However, the data and their interpretation remain controversial [50].

Deriving risk estimates from epidemiological data

The Life Span Study remains the most valuable source of epidemiological data on radiation-induced cancer, although even with this cohort there are limitations in the precision of risk estimates derived from these data.

There remain several fundamental sources of potential uncertainty with epidemiological data, including the Life Span Study.

First, there is the problem of extrapolating moderate dose but high dose rate exposures to low doses and dose rates. Second, there is uncertainty relating to extrapolating cancer risk to the end of a person's lifetime. It is important to be able to distinguish the excess cancers derived from radiation exposure from those that would be expected to arise spontaneously as the person ages. Third, there is uncertainty regarding the validity of transferring site-specific risk estimates, based on the population of the Life Span Study, to another population in which there may be different baseline cancer incidence rates—a phenomenon termed ''risk transport'' [12, 51].

Statistical power and sampling error

In order to detect statistically significant excess risk with an appropriate level of statistical power (*e.g.* 80%), the sample sizes required can be extremely large. Moreover, the excess deaths required to demonstrate a statistically significant excess risk estimate vary inversely with the excess risk. For example, the lower the number of deaths expected per extra sievert of radiation exposure, the greater the number of cases required to demonstrate a significant excess risk in a study. The number of cases required to demonstrate an effect is approximately proportional to the inverse square of the ERR coefficient [12].

Dose and dose rate effectiveness factor

There is potential error relating to the application of the DDREF, which is generally accepted to be 1.5 by the BEIR VII report. This value, however, has been derived from epidemiological data obtained from acute exposures and high dose rates and animal studies demonstrating a curvature in the linear response with increasing dose. Its extrapolation to low doses and dose rates is therefore an additional source of potential error when deriving radiation risk estimates [51].

Other sources of error

As with any epidemiological study, there are further sources of potential error that need to be understood and attempts made to assess their relative significance. These include: detection error (classification of cancers as non-cancers) and confirmation error (classification of non-cancers as cancers); selection bias, which in the case of the Life Span Study cohort involves selecting for follow-up individuals who are inherently less radiosensitive by virtue of surviving the bombings at the outset; and dosimetry errors, which can be classified as systematic or random, *e.g.* relating to the air transport calculation method [51].

Resolving the effects of epidemiological uncertainty

Attempts can be made to assess the relative importance of the various sources of epidemiological uncertainty. One method is termed ''one-at-a-time uncertainty analysis'', and involves evaluating the effect of one variability of uncertainty, *e.g.* selection bias, or DDREF, while keeping other factors constant, *i.e.* using nominal values. This leads to an assessment of the relative importance of identified sources of epidemiological uncertainty.

A more sophisticated approach to quantifying uncertainties in lifetime attributable risk is the Monte Carlo method. This involves repeated random sampling of all the variables of uncertainty. Despite the necessary limitations of epidemiological data as described, major international regulatory bodies have continued to adopt the LNT model for radiation protection policy, suggesting that it remains the ''best-fit'' model for protecting patients and the public from putative radiation carcinogenesis and other stochastic effects. This precautionary principle is naturally counterbalanced by optimising the tangible benefits of ionising radiation. Indeed, the American Association of Physicists in Medicine [52]

recently issued a public position statement in this regard stating that:

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

Patient factors: age of exposure and individual susceptibility

Although much discussion in the radiation protection community has centred on the validity of the LNT model and associated epidemiological methods, what has perhaps been afforded less discussion is the relative importance of individual patient factors to the risk of developing radiation-induced cancer.

The critical questions that need to be considered are:

- the age of the patient at the time of exposure
- the patient's comorbidities
- the patient's sex.

Our knowledge of age-dependent sensitivity to radiation-induced cancer has been enhanced by studies from the Life Span Study cohort. For example, there is clear evidence that, for thyroid cancer, the age of exposure markedly influences the risk of developing cancer in later life. Individuals exposed as adults showed no demonstrable dose response, whereas there was a clear dose–response relationship for individuals exposed as children (ERR/Sv=9.5 for those exposed under 10 years old, and 3.0 for those exposed at ages 10–19 years) [53].

There are two mechanisms at play to explain the ERR observed in individuals exposed as children: first, the greater number of years available for a cancer to develop; and second, the inherent increased radiosensitivity of tissues in children, which necessarily will contain a larger proportion of stem cells and growing cells, which are likely to be cycling through G2 phases of the cell cycle. Similarly, patient comorbidities will influence the relative effect of a given radiation dose in inducing subsequent cancer, as the life expectancy may be affected, and therefore the number of years available for a cancer to develop will be reduced.

For example, in a study by de González et al [54], estimates of ERR were performed for patients with cystic fibrosis receiving annual chest CT based on organ-specific lifetime risks derived from Life Span Study data. In this chronic condition, if mortality is assumed at 36 years, which is the approximate current median survival, ERR of cancer is 0.02% in males and 0.07% in females. However, if a higher median survival of 50 years is used, as is projected with advances in treatment in the next two decades, then the risk of radiation-induced cancer rises substantially to 0.08% in males and 0.46% in females. The higher ERR in females relates to a higher risk of thyroid cancer, and the high radiosensitivity of breast tissue. Although this is still a relatively low lifetime risk, it does illustrate how age at exposure, comorbidities and the sex of the patient should all be taken into consideration when justifying a radiation exposure.

Genetic factors may influence the ERR estimates; however, these are often organ specific, *e.g. BRCA1* and *BRCA2* genes, and are not deemed to sufficiently alter the population risk estimates as they have low penetrance and are relatively rare in the population.

Environmental factors probably have the greatest effect with respect to confounding the data on radiation-induced cancer. For example, smoking tobacco is a major confounding factor for lung and bladder cancers. This is of great relevance to the Life Span Study cohort as described, as risk estimates are derived which do not necessarily take into account the confounding environmental risk factors in the populations for which the risk extrapolation is performed.

Using epidemiological data to make individualised risk estimates

The limitations of deriving estimates for ERR from our current methods of epidemiological study nevertheless hinder the development of robust and reproducible dose limits which can be applied to multiple cancers and patients.

The alternative—and preferable—approach would ideally be patient-specific risk estimates for cancer and other effects to assist clinicians in making real-time decisions about diagnostic radiation use [55–57]. This would enable patients and clinicians to fully realise the myriad benefits of modern diagnostic radiology techniques, while being more fully informed of accurate individualised and meaningful risk estimates for cancer induction.

However, when some authors have developed such algorithms for point-of-use decision support, the fundamental reality of basing their risk estimates on values derived from the BEIR VII report with its inherent limitations is compounded by additional sources of error attributable to the specific models used. For example, Alessio and Phillips [56] have developed a paediatric CT dose and risk estimator which provides some quantification of individual risks associated with CT examinations.

However, the sources of error associated with deriving CT effective doses, such as variability in the dose length product to effective dose conversion factors, is compounded by the potential sources of error associated with the quantitative risk estimates in the BEIR VII report. Alessio and Phillips [56] concede that the resultant error in their model may be as high as 300% when these factors are considered.

Conclusion

There is considerable, though not universal, consensus in the radiation protection community that radiation-induced cancer can occur at the doses and dose rates

encountered in diagnostic medical radiation. Although little epidemiological evidence exists for the precise shape of the dose–response curve at radiation doses <0.15 Gy, mechanistic radiobiological data would support the conceptual canonical theory of a single electron track potentially inducing cancer.

Although some theories of radiation risk predict even higher risks at low doses, this LNT model is among the more conservative estimates.

It is prudent that the LNT model should continue to be used as the basis for radiation protection policy, including that which is applicable to diagnostic radiology. There is no consistent evidence to support a departure from the LNT model, either by introducing a threshold level of ''safe'' radiation or by altering the shape of the LNT curve at low doses. Indeed, although the existence of departure from linearity may be seen in certain instances, as both upwardly and downwardly curving slopes are possible (Figure 1), the net effect may be best described by a linear curve. At any rate, the precautionary principle should hold, as there may be as yet uncharacterised risks from diagnostic radiation, particularly with regards to other organ risks. For example, there is increasing concern about potential cardiovascular and renal risks from radiation sources [58]. Good patient care should, therefore, indicate erring on the side of caution when there is uncertainty, yet not unduly alarming patients who naturally may have much potential benefit from the applications of diagnostic radiology. For this reason, continuing with the LNT model seems the most prudent course of action.

In summary, the LNT model still remains the most robust model for making decisions about medical radiation exposure *vs* cancer risk, and one of the safest. It should, however, be used judiciously in conjunction with general dose reduction strategies from newer technology and increased use of protocols and patient-specific information to balance the (probable, but uncertain) risk of low-dose radiation with regards to cancer induction against the tangible immediate benefits of CT within the population, *e.g.* in cases of head injury.

Before these individualised risks can be communicated with any degree of confidence to the radiation protection community and patients, the current default position of using the LNT model underpinned by the available epidemiological data (with their inherent limitations) would seem to be the safest and most prudent course of action.

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