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Moving from under the lamppost: can epidemiologists and radiobiologists work together?*

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Understanding and evaluating the health effects of prolonged exposure to low radiation doses, as opposed to shorter exposure to higher doses, has still a long way to go. Answers to these questions cannot be provided by epidemiological studies alone, and so the input of radiobiologists to help focus the work of epidemiologists will become increasingly important in the future. This paper discusses the current research status in this field and emphasizes the importance of interaction between radiation epidemiologists and radiation biologists.

Keywords: radiation, epidemiology, radiobiology

Introduction

In the field of radiation risk estimation, it is very often the case that the radiation risks that are of societal interests are not those risks that can be adequately quantitated. Generally, the aim is to understand the health effects of prolonged exposure to low radiation doses, whereas it is possible to quantitate adequately health risks only from shorter exposures to higher doses.

It has thus long been recognized that extrapolation of measured radiation risks to environmentally relevant situations requires information that epidemiological studies, on their own, cannot provide. An important example in this context relates to the shape of the dose–response relation at low doses, which has generated lively debate about low-dose linearity and/or a threshold in dose for radiation risk. Other examples include issues of extrapolation from one radiation type to another, or from one exposure to another.

In principle, this 'extra', non-epidemiologically-based, information required for risk extrapolation, is the domain of radiobiology, either experimental or theoretical. In practice, however, this is rarely the case. For example, although all of the National Academy of Sciences Biological Effects of Ionizing Radiation (BEIR) reports have, to date, included chapters on radiobiology, the contents of these chapters have played a limited, if any, role in the risk estimation parts of these reports.

Why has radiobiology often played little more than a pro-forma role in radiation risk estimation? In part the authors argue it reflects a lack of communication between the disciplines, but in part it reflects the fact that radiobiologists still do not have a complete set of tools for understanding radiation response, particularly for an endpoint as complex as radiation-induced carcinogenesis. In recent years, however, radiobiologists have started to move away from the lamppost – areas that are comparatively easy to address – and are beginning to look at the hard mechanistic questions which are needed for interpreting and extrapolating epidemiological results.

What tools are available for analysing quantitative radiation response data?

At one extreme, most large-scale epidemiological analyses of quantitative radiation-induced carcinogenesis data, such as those in past BEIR reports, have been based largely on empirical, descriptive, modelling of the epidemiological data.

At the other extreme, there has been some recent interest in so-called 'biologically-motivated' models, designed to provide realistic quantification of all the relevant steps from energy deposition to the appearance of, say, cancer. In this context, the parameters of

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the model have a biological interpretation and could, in theory, be evaluated directly from experimental data.

Clearly neither of these extreme situations (no radiobiological input used, or complete radiobiological mechanisms assumed) is currently satisfactory. This paper discusses a middle way that is both useful and practical, where information derived from one discipline is used to augment specific areas of uncertainty in the other discipline. Thus, concepts derived from one discipline can be used to facilitate research in the other.

These various possible approaches are discussed in the following sections.

Purely mechanistic, biologically-motivated approaches

Biologically-motivated analysis techniques are designed to provide realistic quantification of all the relevant steps from energy deposition to the appearance of cancer. In this context, the parameters of the model have a biological interpretation and could, in theory, be evaluated directly from experiment.

An example of such an approach for the carcinogenesis process is the two-stage stochastic model with deterministic growth of normal cells.[1] Such approaches to radiation risk estimation have been proposed and critically discussed by various authors.[2–4]

While recognizing that application of biologically-motivated risk models is a highly desirable goal, such approaches have not, as yet, reached the stage where they could be used for realistic risk assessment. This is because of the complexity and multiplicity of the processes involved in radiation carcinogenesis, as well as the many gaps in our knowledge concerning the most basic relevant processes. Currently only a few related models of the carcinogenic process have been formalized (two or more stages followed by clonal expansion[1]), and not model validation has yet been achieved.

If such models were complete and validated, they could represent the optimal analytic tool for cancer risk estimation based on epidemiologic data. However, the models are currently only highly schematic in nature, and almost certainly reflect incomplete or inaccurate views of the process of radiation-induced carcinogenesis. Specifically, there is a rapid rate of change of the paradigms for the carcinogenic process in general, and radiation carcinogenesis in particular. For example, the potential significance of delayed instability – which is quite inconsistent with currently formalized biologically-motivated models – was not apparent until the last few years. In this light, the use of the current generation of biologically-motivated analytic models would, at this time, be premature and potentially misleading.

Purely empirical (descriptive) approaches

In an empirical risk model, *a priori* assumptions are made about either the shape of the exposure–response function or the factors that influence risk. In its most general characterization, only minimal assumptions are made about the structure of the risk model. It is this generality, as well as the absence of any intrinsic underlying link to a biological mechanism of disease occurrence, that leads to the characterization of the modelling approach as empirical or descriptive.

The empirical modelling approach also allows for evaluation of diverse factors, such as sex, age, exposure, et cetera, the importance of which can be evaluated through formal hypothesis testing. Cancer occurrence is undoubtedly a complex process. Factors are included in a model based on statistical testing; therefore, by necessity, the empirical approach results in models which are relatively crude, and are at best rough approximations of the true risk patterns, with very limited scope for extrapolation.

A hybrid approach: empirical modelling supplemented with relevant mechanistic information

In this approach, radiobiological data or concepts can be used to guide empirical epidemiological analyses in specific areas where there is uncertainty, but no general model for, say, radiation-induced carcinogenesis, is assumed.

This hybrid approach can work in either direction, with radiobiology facilitating radiation epidemiology, or vice versa. In one direction, radiobiology can identify areas of model uncertainty that need elucidation from human data, and specific epidemiological studies can be designed to address these uncertainties. Conversely, data from epidemiological studies may also point to specific areas of uncertainty that can be addressed through laboratory and mechanistic studies.

Examples of the hybrid approach

This sections gives some examples of how this hybrid approach has worked successfully in the past, while the Discussion describes some areas where this approach might fruitfully be used for future research.

Radon versus radon progeny as the principal causative factor for lung cancer in miners

Metal mining in the Erz Mountains has long been known to cause 'Bergkrankheit' or 'Mountain disease'.[5] By the 1930s, it was becoming clear that the respiratory problem encountered by the miners was lung cancer. While formal epidemiological studies were not carried out, reports document that, in these years, perhaps 50% of miners eventually died of lung cancer.[6] While some investigators suggested that chronic irritation from dust exposure, metals in the

ore (particularly arsenic) or genetic susceptibility may be responsible, there was recognition by 1932 that radioactivity was a primary culprit.[7]

However in 1944, Lorenz reviewed results of experimental studies of X-ray and gamma-ray exposure and concluded that there was insufficient total absorbed energy from radon to cause the lung cancer observed in the German and Czech miners and suggested that other factors must play a role.[8] Thus a situation occurred where the observational data suggested the amount of lung cancer in miners could not be explained by known causes, including exposure to radon.

The issue of radiation dose to the lung was addressed by Bale[9] and Bale and Shapiro,[10] who identified that the radiation dose to the bronchial epithelium from radon decay products was about 20 times that from radon, with most of the dose coming from alpha particles.[11] These analyses suggested that exposure to radon and its progeny was sufficient to account for the lung cancer in miners and that exposure could pose a substantial health risk to underground miners, although the precise level of risk was still, at that time, very uncertain.

The inverse dose rate effect for radon

When a given dose of sparsely ionizing (low-LET) radiation is protracted, whether by lowering the dose rate or through increased fractionation, the biological effect is either unchanged or decreases, because of the possibility of sublethal damage repair during the irradiation. However, it has become increasingly clear that densely-ionizing (high LET) radiations such as neutrons and alpha particles exhibit an 'inverse dose-rate effect' for oncogenic endpoints. Specifically, for a given dose or exposure, as the dose rate is lowered, the probability of oncogenesis increases. This inverse dose-rate (IDR) effect, clearly involves protraction effects other than those of sublethal damage repair – this latter being the dominant effect of protraction at low LET.

The role of dose rate as a modifier of the dose-response relationship for radon-exposed miners has long been considered in epidemiologic studies. In one of the first evaluations of the Colorado Plateau uranium miner data, Lundin *et al.*,[11] found no significant variation of the exposure–response relationship with exposure rate. However, Hornung and Samuels, using a later 1977 follow-up, demonstrated a significant IDR effect, with the lung cancer risk at equal exposure greater in miners exposed at lower exposure rates.[12] These results supported an earlier analysis of Czech miners which also reported greater effects among miners exposed at lower exposure-rate.[13]

Independent of these early radon miner studies, this IDR effect was observed from the late 1970s in laboratory animal experiments for neutron-induced and charged-particle-induced carcinogenesis,[14–17] and for life-shortening experiments with neutrons.[18,19] These animal results prompted corresponding studies with quantitative *in vitro* oncogenic transformation systems exposed to neutrons and charged particles;[20,21] these *in vitro* studies also documented significant IDR effects.

In turn, these laboratory results stimulated theoretical studies into possible mechanisms.[22–24] Although the exact mechanisms were not, and still are not, fully elucidated, some general – and model-independent – principles became clear which must control the general patterns of how the effect changes with differing doses and dose rates. Specifically, at low doses of high-LET radiations, where target cells (or small groups of target cells) are subject to an average of much less than one alpha particle (or neutron), there can be no dose-rate effect of any kind, as the target cells would not be 'aware' of any dose protraction. At higher doses, of course, dose-rate effects are possible.

In the late 1980s, again independent of the radiobiological investigations, stronger evidence for IDR effects in miner studies became apparent. In comparisons between epidemiological studies involving different average radon-daughter exposure rates, Howe *et al.*[25] and Darby and Doll[26] inferred an IDR effect. Within a particular epidemiological study, an IDR effect was reported by Hornung and Meinhardt,[27] analysing lung cancer rates in a 1982 follow-up of the Colorado uranium miners, by Tomášek *et al.*[28] for Czech miners, and also by Xuan *et al.*[29] in Chinese tin miners exposed to radon daughters. In recent joint analysis of eleven cohorts of miners exposed to radon, Lubin *et al.*[30] clearly demonstrate the existence of a statistically significant IDR effect.

While the IDR effect was clearly evident in these epidemiological studies of miners, what did not emerge from these analyses was its dose dependence; generally speaking, at lower miner exposures, the statistics become poor and so, unless specifically looking for an exposure dependency to the IDR effect, it would be unlikely to be seen. In the light, however, of the radiobiological analyses, the authors of the large study of eleven miner cohorts re-examined their data,[31] and did observe a decrease in the IDR effect with decreasing dose, until it essentially disappeared at exposures corresponding to less than one alpha particle traversing target lung cells.

Such a finding is relevant to the extrapolation of risk from miner data, where generally there is an IDR effect, to domestic exposures where one would not be expected. Risk projection models for the estimation of risk from residential radon exposure can account for a diminution of the IDR effect either by explicitly modelling the phenomenon, developing the projection model using only low exposure data where the effect is minimal, or developing the projection model using only residential data.

Low-dose extrapolation

A common problem in epidemiology is to define the dose–effect relationship at low doses, and risk assessors face the even more daunting task of extrapolating to low doses where there are no useful data. Realistically, with current techniques, radiation-epidemiological studies on their own are unlikely to provide quantitative conclusions below low-LET doses of about 200 mGy,[32,33] with the possible exception of studies of childhood cancer after *in utero* irradiation, where conclusions at doses as low as 10 mGy may be possible.[34]

A common assumption is that, at low doses, a linear relationship is appropriate down to arbitrary low doses – a concept often described as 'linear/no threshold'. Is this linear extrapolation correct? The biophysical rationale involves at least the following steps

(*a*) Radiogenic cancer induction is causally related to radiation-induced damage in a single cell (i.e. cancers are of monoclonal origin),

and considering here only the low-dose situation where

(*b*) the dose is so low that the mean number of radiation tracks in the target of interest (e.g. the nucleus or a group of cells) is < 1; in this situation, it follows that a change in the dose simply results in a proportionate linear change in the number of targets subject to a single energy deposition event

and so if

(*c*) a single energy deposition event can produce, with finite probability, the critical damage necessary in a cell (see (*a*)) to initiate the sequence of events leading to cancer

then

(*d*) the dose-yield relationship will be linear at low doses for production of the critical damage necessary in a cell to initiate the sequence of events leading to cancer, and the dose–response relation for low-dose radiation cancer induction will be linear with dose, and consequently without a threshold in dose.

Of course, the steps in the argument contain uncertainties; for example (*d*) presupposes that an organ with, say, one cell containing critical damage is *n* times less likely to show a cancer than if it had *n* critically damaged cells. Is this correct? There is no current evidence to the contrary. The logic behind (*c*) presupposes some specific energy deposition (say, some number of adjacent ionizations) that is required in a cell to produce the critical damage in that cell; because of the stochastic nature of ionizing radiation energy deposition, no matter what the dose, there will be a finite possibility that any given cell will receive that critical energy deposition – and at low doses, this probability will simply decrease linearly with dose. This argument should be valid at low- and high-LET.

Finally, (*a*) presupposes a monoclonal origin of cancer, the use of molecular-genetic approaches to the study of the monoclonality of tumours has strongly complemented the traditional approaches to this question, and the evidence that the great majority of cancers are of monoclonal original is becoming increasingly strong.[35,36] The uncertainty here relates to the assumption that a cell population is homogeneous with respect to a particular marker. By the time a tumour is detected it will have undergone extensive genetic changes, and so selection of subclones might have occurred, and assessment of clonality at that time might not then reflect the earliest events in carcinogenesis.

Extrapolating from gamma-rays to X-rays

By and large, most radiation risk estimates are based on analysis of A-bomb survivors who were exposed primarily to an acute gamma-ray dose. The photons to which they were exposed were of high energies, with a peak fluence at around 0·1 MeV, but extending out to about 1 MeV.

At about 50 keV, the primary mode of interaction of photons with biological material changes from Compton scattering (at higher energies) to the photoelectric effect (at lower energies). Thus most of the dose to A-bomb survivors would have come via Compton scattering. On the other hand many other major radio-epidemiological studies involved lower-energy X-ray sources. Both the tinea capitis[37] and multiple-fluoroscopy pneumothorax[38] studies involved 70–100 kVp X-rays, and thus a significant component of photoelectron dose. By further contrast, mammograms are now generally performed with $\sim$28 kVp X-rays. Simple radiobiological calculations allow the low-dose relative biological effect to be calculated for these different photon fields.

Typical calculated[39] low-dose relative effects are Hiroshima/Nagasaki, 0·65; 70–100 kVp X-rays, 1·0 28 kVp X-rays, 1·3. These ratios are in agreement with much *in vitro* data for chromosomal and oncogenic endpoints.[40–43] Such differences are unlikely to be detectable in comparisons among different studies, but factoring them in should allow the significance of other variables to be better elucidated.

This example typifies a particular important class of interaction between radiobiologists and epidemiologists, relating to situations where it is very unlikely that direct epidemiological studies will yield the desired information. In this case, for example, a direct epidemiological study of the cancer risks of mammograms is impractical, because of the low dose/risk involved, yet the probable increased biological effectiveness (per unit dose) of monographic X-rays relative to gamma-rays should be considered in risk assessment from mammographic X-rays.

The linear-quadratic formalism

The linear-quadratic formalism has long been a staple for radiation epidemiologists to fit dose–response data. Its use has often been thought simply to represent a convenient representation – the first two terms of a power series – of monotonically increasing dose–effect data.

By contrast, in recent years, it has been shown that the kinetics of the different pathways by which initial radiation damage is processed can be linked to dose–effect relations for measurable endpoints,[44] and this linkage allows a mechanistic interpretation of measured dose–effect parameters.

For low or intermediate doses, almost all kinetic reaction-rate models predict linear-quadratic (LQ) behaviour, with the same form of the generalized Lea–Catcheside G factor which accounts for repair during dose protraction. Specifically, the effect, E, is related to dose, D, as

$$E = \alpha D + G\beta D^2 \qquad (1)$$

where G is the generalized Lea–Catcheside function,

$$G = (2/D^2)\int_{-\infty}^{\infty} \dot{D}(t)dt \int_{-\infty}^{\cdot} \mathrm{e}^{-\lambda(t-t')}\dot{D}(t')dt' \qquad (2)$$

Here $\dot{D}$ tracks the dose rate as a function of time during the irradiation time, t, and λ is a characteristic repair constant.

The kinetic reaction-rate models which underlie the LQ in turn supply mechanistic interpretations for the LQ parameters α and β. In the context of carcinogenesis, the second term in equation (1) corresponds to two-track production of exchange-type chromosome aberrations, such as translocations, whilst the first term in equation (1) corresponds to one-track production of small genetic mutations.

The LQ formalism essentially refers to damage induced in single cells. Is this relevant to cancer, a multi-cellular phenomenon? In fact, as has been discussed, as more sophisticated techniques become available, it is becoming apparent that not only the great majority of haematopoietic cancers, but also the great majority of solid tumours, are of monoclonal (i.e., single cell) origin.

There is now a quite firm connection between molecular mechanisms and the LQ formalism of equations (1) and (2),[44] and this formalism can no longer be thought of as simply a useful power-series approximation, as had often been the case in its past usage. Despite all the uncertainties and limitations involved, this molecular connection is, the authors would suggest, a considerable advance.

Haematopoietic versus other cancers

It is possible to take advantage of the mechanistic interpretation of the LQ formalism to generate the most appropriate dose–response relations for analysing specific radiation carcinogenesis data.

In recent years, it has become increasingly clear that most leukaemias and lymphomas involve specific chromosomal translocations, probably associated with oncogene activation;[45–47] by contrast, most solid cancers are associated with comparatively small-scale mutational damage associated with inactivation of tumour suppressor genes.[48]

As discussed earlier, because of the kinetics underlying the LQ formalism, at low-LET, it is possible to associate the quadratic term of the LQ with the production of exchange-type chromosomal aberrations such as translocations, and also to link the linear term of the LQ with the production of small mutations.

From these considerations, at doses that are not too high, the LQ formalism predicts a linear relationship between risk and dose for radiation-induced solid cancers, and a quadratic relation between risk and dose for low-LET radiation-induced haematopoietic cancers. These predictions are consistent with observed data,[32] and probably represent a more useful approach to understanding dose–effect relations than extensive fitting of various power series to radiation epidemiological data.

From equation (1), these considerations also allow clear predictions about protraction effects for low-LET radiation. Specifically, there is no dose-rate-dependent repair term to the linear component in the LQ, implying that X- or gamma-ray induction of solid cancers should be independent of dose rate, and no dose-rate correction factors for repair should be used. By contrast, the quadratic term in the LQ is modified by the Lea–Catcheside dose-rate factor, and thus protraction of the dose would be expected to reduce the risk of low-LET radiation-induced haematological cancers relative to an acute exposure.

Discussion

Interactions between radiation epidemiologists and radiation biologists are going to become increasingly important as the field focuses more and more on the effects of low doses of radiation. There are a number of broad areas in which radiobiological input could assist epidemiological analysis and extrapolation, some of which are now listed.

(*a*) *Molecular biomarkers.* There are no validated biomarkers which provide an exclusive fingerprint of past radiation exposure, though several have been suggested. Such fingerprints would provide a dramatic increase in the power of low-dose studies.

(*b*) *Cofactor effects.* A mechanistic formalism which describes the joint association of radiation with other relevant carcinogens, such as smoking, or

chemical exposure, would provide a coherent framework for epidemiological studies involving radiation and other carcinogens.

(*c*) *Low dose effects*. If the various uncertainties associated with the radiobiological rationale described earlier for the 'linear/no threshold model' could be addressed, low dose extrapolations from available data would be much more credible. For example, whether the per-cell probability of low-dose tumorigenesis following 'critical' damage to a cell is independent of the number of damaged cells, remains an unanswered though much discussed question.

(*d*) *Genetic instability*. There is currently much interest in the notion that radiation damage may be primarily manifest in cells many generations subsequent to those exposed to the radiation. Currently the available studies are not quantitative, nor are they consistent, but the effect on dose–response relations of such mechanisms remains to be elucidated.

In addition to such radiobiological input, there is another class of interactions which inherently involves both radiobiologists and epidemiologists. This is the area of genetically-based radiation sensitivity. For example, studies of whether the 1–2% of *AT* heterozygotes represent a sensitive subpopulation for radiation-induced cancers would not be possible without active input from both radiobiologists and epidemiologists.

Conclusions

Both in radiobiology and in radiation epidemiology, purely phenomenological or statistical approaches to dose–effect relations have, in the authors opinion, gone about as far as they can go.

Radiobiological identification of damage pathways on the molecular level will be increasingly important. However, qualitative molecular investigations, despite their current popularity, are not likely to be very useful either. The question is not whether a given gene product has some effect or shows some response to radiation; the question is what damage pathways are *dominant* for the important biological endpoints. This is the current challenge of molecular radiobiology.

From the epidemiological standpoint, with increasing focus on lower doses, radiobiological input is becoming more and more important. There is still a long way to go before a grand unified 'biologically-based' model of radiation-induced cancer will be of practical use, so it is important that radiation epidemiologists identify areas of major uncertainty, to allow radiobiologists to focus their attentions appropriately, and to use radiobiological input in those specific areas where it is needed.

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