The Risk Linked to Ionizing Radiation: An Alternative Epidemiologic Approach

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Radioprotection norms have been based on risk models that have evolved over time. These models show relationships between exposure and observed effects. There is a high level of uncertainty regarding lower doses. Recommendations have been based on the conservative hypothesis of a linear relationship without threshold value. This relationship is still debated, and the diverse observations do not allow any definitive conclusion. Available data are contradictory, and various interpretations can be made. Here we review an alternative approach for defining causation and reconciling apparently contradictory conclusions. This alternative epidemiologic approach is based on causal groups: Each component of a causal group is necessary but not sufficient for causality. Many groups may be involved in causality. Thus, ionizing radiation may be a component of one or several causal groups. This formalization reconciles heterogeneous observations but implies searching for the interactions between components, mostly between critical components of a causal profile, and, for instance, the reasons why specific human groups would not show any effect despite exposure, when an effect would be expected. *Key words*: norms, radiation epidemiology, radiation protection, radiation risks, risk factors. *Environ Health Perspect* 109:877–880 (2001). [Online 15 August 2001]
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Setting limits for exposure doses to prevent adverse outcomes in humans is an old debate in radioprotection (*1*). Various threshold values have been proposed. Historically, the first permissible dose proposed was linked to deterministic effects of ionizing radiation. These values were around 500 mSv (50 rems). The threshold doses at which nonstochastic effects appear were based on these figures. They have not been modified to date and represent the dose limitation levels for isolated organs.

Given recommendations from the National Council of Radiation Protection (NCRP), in 1956, the International Commission on Radiological Protection (ICRP) adopted the proposed dose limits, expressed as the following simple equation for occupational exposure and assuming that people under 18 are not occupationally exposed: The limits for occupational dose accumulated at various ages is the dose $D = 5 (N - 18)$, where N is the age in years, and D is expressed in rems (*2*).

The risk level for the population was proposed to be one-tenth of the occupational risk, computed for 1 year (i.e., 0.5 rems/year) (*2*). It is therefore not only stochastic effects that will dominate radioprotection, but, more decisively, it is the cumulative aspect of radiation risk, especially for cancers.

The cumulative risk model allows one to take into account all radiations, even the very small ones for individuals and for a group. The consequences of this new concept had an enormous impact for the nuclear energy production industry, for example, which now faces great difficulties as a result of this risk concept (*3*).

With the ICRP 26 (*4*), the stochastic (i.e., cancer) and gonadic risks became the basis of radioprotection. Indeed, as the first data on cancers following the bombings of Nagasaki and Hiroshima became available, the ICRP (*2*) proposed the computation of the total body equivalent dose on the basis of a total cancer risk per organ, and a gonadic risk, the sum of weighting factors being equal to 1.

This computation supposed that *a*) there is no threshold level of risk at the level of organs, *b*) there is a hierarchy of risk between organs, *c*) there are two reference effects—stochastic effects of fatal cancers and a complementary genetic risk, and *d*) there is a simple relation between risk and ionizing radiation based on an "absolute risk model." A known quantity of exposure induces a known quantity of effect, so a change in the baseline incidence rate in nonexposed persons does not affect the magnitude of increase in risk in exposed subjects. But this reasoning has been challenged over time.

Analysis of the Normative Approach

Normative recommendations. Except for the induction of leukemia and bone cancers, the epidemiologic model to consider is a relative risk model (*5*). A known quantity of exposure modifies the outcome by a certain multiplicative effect. A change in the baseline incidence thus affects the level of outcome difference.

This model has several consequences: On one hand, assuming that the cancer rates increase over time, this new model implies an increased risk difference. On the other hand, the relative risk model means that ionizing radiation is a cofactor of cancers, which was not necessarily the case for an absolute risk model. Ionizing radiation may be considered a component, which modifies proportionally a general risk, whereas it is the specific appearance rate of the general risk that determines the noxious action of radiations. In other words, it is the conjunction of several elements that explains the effect of ionizing radiation, among which is the background rate of cancer for the corresponding organ.

Fundamental research. Carcinogenesis is a complex phenomenon that includes multiple steps, some of which are sequential (*6*). This is consistent with the cofactors necessary for carcinogenesis.

Mutations necessary for carcinogenesis may be linked not only to the action of an external mutagenic factor, but also to increasing instability of the nucleus (e.g., mutating phenotype due to the loss of p53) (*7*). The indirect action of ionizing radiation is currently under intense scientific scrutiny. If the action of ionizing radiation is indirect, this will modify the relationship between exposure and effect, reinforcing the cofactorial aspect.

The initial lesion consists of DNA double-strand breaks, stabilized quite rapidly within 2 hr. Why does such a lesion induce chromosome aberrations a few generations later (*8*)? The process is not well understood. The concept of an indirect action of ionizing radiation on carcinogenesis is therefore reinforced. Kennedy and Little (*9*) showed more than a decade ago the dissociation between causes and effects in ionizing radiation.

Cancer transformation cannot be dissociated from apoptosis of the progeny of irradiated cells (*10*): This occurs belatedly, around the 12th cellular generation, following a mechanism that is not yet understood that includes antiapoptosis processes that stop progressively according to a biologic apoptosis clock. Understanding the mechanisms of

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apoptosis is necessary to understanding cancer transformation (*11*).

Suprasensitivity to low doses underlies the hypothesis of supralinearity between exposure and effects at the same dose, and reflects the effect of cellular adaptability to recurrent radiations (*12–15*). In addition, this adaptability combines with weaknesses in the defense mechanisms of the nucleus against other genotoxic elements (*16*). This is the price organisms pay for adaptation.

Research also focuses on nuclear instability before cancer transformation. We know about instability after the loss of control of the p53 system. The idea of nuclear instability goes beyond this and proposes an early generalization of this instability: Instability would be the cause, not the effect, of genetic modifications necessary to cellular transformation and would be expressed progressively through increasing cellular division (*17*). But it may also be expressed itself along with cellular aging (*18*).

Another emerging notion is that of indirect genetic effects on cellular cytoplasm, or even on the cytoplasm of neighbor cells. The genotoxic target of ionizing radiation is therefore larger than the genome itself (*19*).

Epidemiology. Stochastic effects are observed during exposure at higher doses of ionizing radiation than those encountered in a normal environment. Indeed, from single or cumulated doses above 250 mSv, observations are rather consistent. In contrast, observations of effects from lower radiation levels are surprisingly heterogeneous and contradictory.

An interesting example is the disparity of findings within a Canadian study of the risk of breast cancer among women irradiated by fluoroscopies during the treatment of pulmonary tuberculosis (*20*). The results of all provinces are consistent among each other, except Nova Scotia, which shows the most important risk despite similar quantities of irradiation (relative risks per Gray are, respectively, 1.20 and 3.03). The difference between Nova Scotia and other provinces has not been explained. One hypothesis might be the difference due to a higher dose delivery rate during examinations in Nova Scotia.

Debates exist about threshold values and the relationship between exposure and stochastic effects (*21*). One point of view is that the stochastic risk is likely to have a threshold level, which would be between 100 and 250 mSv (*22*).

Another is that the stochastic risk has no threshold level. The relationship may be supralinear (increased effects at low doses); it may be linear (*23*); or it may be quadratic (minimized effects at low doses) (*24*).

Current recommendations propose standards that account for a linear conservative risk without threshold value, together with a stochastic model computed on a quadratic basis using the dose/dose-rate effectiveness factor relationship (DDREF) = 2 below 0.2 Gy (i.e., a proportional decrease from the linear extrapolation without threshold value computed at high doses) (*25*). But the relationship between very low exposure and effect for residential radon is controversial (*26*). In this respect, the controversy between the ecologic study of Cohen (*27*) and case–control studies is interesting. Cohen (*27*) explains the discrepancy between these studies as proof of the absence of linearity between exposure and effect in very low radon exposures. On the other hand, Lubin and Boice (*28*) think that the discrepancy is caused by the "epidemiologic fallacy" (*29*). Controversies over the weaknesses of ecologic studies have been discussed by many authors (*30*,*31*). Other cofactors may explain the discrepancy. For example, smoking is an important cofactor (*32*). The effect is neither additive nor multiplicative, but somewhere in between. Smoking limits the risk of radon versus nonsmoking habit [relative risk $(RR)_{\text{no smoking}} = 1 + 0.0103$ working-level month (WLM); $RR_{\text{smoking}} = 1 + 0.0034$ WLM]. Other explanations have been proposed, such as latitude or rural/urban status (*33*,*34*).

Discussion

Rothman (*35*) defines the cause of a disease "as an event, condition, or characteristic that plays an essential role in producing an occurrence of the disease" (p. 11). He also argues that the appearance of a disease is linked to a process involving several components, each of them being necessary but not sufficient to cause disease. When we examine the complex, sequential process of cancer, this hypothesis is obviously more plausible than the unique causality determining a unique effect. Causality seems therefore to be multiple. In each sufficient causal group, there would be a number of necessary but not sufficient components, except in the case of a causal group that comprises a single component (Figure 1).

If one component is missing, the causality disappears. In this approach, the less frequent component will be the limiting factor of causality. Given relative scarcity of this component compared to others, it will be a determining factor. From this point of view, the cumulative importance attributed to all the necessary factors of causality can obviously exceed 100%. The paradigm of this approach lies in the fact that the component that appears to be the most noxious and the most determining is actually the least important because of its scarcity in the causal group.

Rothman (*35*) proposes that "each constellation of component causes is minimally sufficient (i.e., there are no redundant or extraneous component causes) to produce the disease. Component causes may play a role in one, two or three causal mechanisms. … Thus, the apparent strength of a cause is determined by the relative prevalence of component causes. A rare factor becomes a strong cause if its complementary causes are common" (p. 12). The rare factor is a critical component. In contrast, a frequent factor becomes of minimal effect if its complementary causes are infrequent.

Difficulties lie in the exposure and risk assessment of all contributing toxic substances of environmental concern (*36*). When the Rothman model is applied to the risk induced by ionizing radiation, some inconsistencies or controversies in the observations may be better understood. The same may be said of the application of fundamental research. Difficulties may be resolved by seeking other components of different causal groups in which ionizing radiation is one of the factors. Risk assessment should take into account all the factors, provided that the importance of each individual factor cannot be assumed. In other words, the problems will not be resolved completely by considering only the ionizing radiation.

Examples

In a case–control study, in which Stewart et al. (*37*) observed an increase of leukemia in children exposed *in utero* to simple X rays, a controversy arose immediately because the dose required for risk of leukemia was decreased by at least an order of magnitude (10 times less, dose around 10 mSv) (*38*). Surprising in this debate was the position of MacMahon (*39*), who found an effect of the same size in a cohort study of 700,000 children, but refused to admit the causality, arguing first the presence of an unknown confounding factor (*40*). MacMahon (*41*) stated that three observations seemed incompatible with the results of Stewart: first, the observed cancer risks of the children irradiated *in utero* at the time of the atomic bombs; second, a significant difference between the absolute risk coefficients for infants exposed prenatally and those exposed after birth; and third, the finding of an equivalent increase in solid cancers, which seemed to him uncharacteristic. In fact, differences seem to exist between childhood and adult

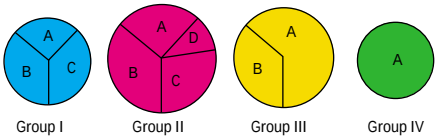

Figure 1. Causal groups. A, B, C, and D are necessary but not sufficient components, except for Group IV, where A is a sufficient component. Adapted from Rothman (*35*).

cancer sensibility, cancer latency, types of tumors, and period of cancer sensibility during pregnancy. There is also limited information about cancer risk for children irradiated early in postnatal life (*42*). Doll and Wakeford (*43*) and Boice and Miller (*44*) studied the elements in favor of causality and related uncertainties in the case of leukemia in children exposed *in utero*, with contrary conclusions about a causal epidemiologic association between prenatal irradiation and childhood leukemia and cancer.

The finding in the nuclear industry, at Oak Ridge National Laboratory (*45*), of increased mortality due to leukemia among the workers was strongly debated (*46*). The results at the Oak Ridge National Laboratory led to investigations of an unknown confounding factor (*47*). A better appraisal of the healthy worker effect and the observation of a higher susceptibility to radiation with age over 45 have been proposed to explain certain results of the Oak Ridge study (*38*). Studies about occupational radiation exposure in Canada show similar results (*48*) (with an estimated excess RR of 3% per 10 mSv), whereas other observations failed to show any harmful effect.

Gardner et al.'s (*49*) hypothesis that childhood leukemia is attributable to the father's low occupational exposure to radiation was the center of an intense controversy (*42*). Geographic disparities (*50*) together with confounding factors (*51*) were proposed as explanations for the cluster observed.

The cluster found in Berlin showing an increase in the rate of Down syndrome in children of mothers exposed to the Chernobyl nuclear accident was explained by an iodine deficiency in these populations (*52*).

The study of susceptible and fragile populations is essential in this respect because the genetic aspect is obviously one of the components of the causal groups. Persons with a heterozygous gene for ataxia telangectasia (*53*), or carrying a gene for Li-Fraumeni syndrome (*54*) are examples of susceptible populations. Lavin et al. (*55*) found higher sensitive subgroups of breast cancer patients.

Analyses of studies of the survivors of nuclear bombings are not always consistent *(56–58)*. It is important to note that the controversy occurs because of heterogeneity of effects in a possibly biased cohort compared to exceptionally healthy persons. Stewart (*59*) found a selection bias in the Life Span Study Cohort. A susceptibility difference to radiation cancer effects in the exposed population may be explained by age (cutoff at ± 50 years of age) and by amounts of irradiation (threshold for excessive marrow damage). Thus, atomic bomb survivors may not be representative of populations exposed to radiation by other means (*38*): "As a result of these biases, atomic bomb data are not a reliable source of cancer risk coefficients, but they can still be used to study factors with immune system associations" (p. 96).

New concepts regarding the oxidative cellular stress induced by irradiation, which produces free radicals, involve oxidative stress in complex mechanisms, which is not only linked to the genetic profile, but is also common to other toxicologic mechanisms. In the same way, the production of transmissible cell-to-cell effects, between hit and nonhit cells (bystander effects), and a transmissible effect of an instability phenotype reinforce the theory of necessary but not sufficient nor unique components of a causal group and the necessary synergy with other toxic, physiologic, or genetic components (*19*).

Conclusion

The hypothesis of a causal group with necessary but not sufficient components implies that the hypothesis of a risk without threshold value should be maintained until all the components of the causal groups are defined. Because, in principle, it will never be possible to know all the causal groups and their composition, the hypothesis of no threshold value should be maintained.

It is, moreover, possible that among all the causal groups including the component of ionizing radiation, there is at least one group that includes only ionizing radiation.

The supralinear, linear, quadratic, or other relationship is linked not necessarily to the irradiation itself, but to the combination of various components. If the existence of these components is admitted, one must allow reasonable pessimistic hypotheses because uncertainties necessarily remain in the composition of the causal group.

Eliminating one of the components will lead to the elimination of causal group(s) where this component is present, and therefore a decrease of the global risk associated with the other components of these causal groups may occur.

Research must focus on components other than ionizing radiation, because these factors might be equally important (not restrictive of the effect). It may be possible to operate on these factors to make them become restrictive of the effect. This is reflected by environmental cancer prevention.

The hypothesis of causal groups implies that we must investigate not only the reason for an effect linked to exposure to ionizing radiation, but also the reason for a lack of effect after exposure. In this particular situation, a (partial) eliminated (critical) component must be investigated. This is implicit in the hypothesis that a different restrictive component is included in the same causal group as ionizing radiation.

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