EPIDEMIOLOGY AND CANCER RISK FROM LOW DOSES OF RADIATION

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Introduction

Although ionizing radiation appears to be the most thoroughly investigated single carcinogenic agent, it still poses a problem: the quantitative risk of malignant development following low radiation doses is not known with sufficient accuracy. Most disturbingly, some recent epidemiological studies[3,4,6] seem to suggest much higher cancer risk values per unit dose than the current risk estimates accepted by international and national organizations for radiation protection.[1,5,12] It is commonly stated that the effects of low-dose radiation cannot be demonstrated, on statistical grounds, in small populations. However, this statement is valid only on the tacit assumption that the actual risk is small and constant.

The epidemiological approach has sometimes been criticized on the grounds that it does not prove much because, despite careful design of data collection and analysis, there are often confounding non-random variables that affect the final results. However, the mere existence of 'confounding' factors does not necessarily mean that they are irrelevant to the problem because they could also modify the expression of radiation-induced damage. Development of cancer, initiated by radiation, is a complex process and other factors such as promoters may drastically affect the outcome of the primary effect. Thus there is no good a priori reason to assume that all reliable studies must end up with some universally valid risk estimate consistent with the high-dose studies, expecially those concerning A-bomb survivors. Interestingly, the credibility of the Japanese data base itself has become somewhat questionable because of the uncertainties in the radiation dose estimates.[8]

Population Size and Risk Estimates

To show that ionizing radiation is carcinogenic at low doses is clearly difficult epidemiologically. However, merely the finding that 10 mGy of low-LET radiation can transform cells in vitro with a frequency of up to 10^{-4} (see ref. 2) should make us cautious; remember that there are some 10^{12} cells in the human body that may be targets for malignant transformation. Yet, if the cancer risk estimates of ICRP or UNSCEAR are correct, it is virtually impossible to demonstrate, on statistical grounds, any excess cancer cases in human populations exposed to doses below 10 mGy. On the other hand, if an effect is manifested within a population of some 10,000 people, the current risk estimates may not be universally valid.

The size of a study population must naturally be large enough to allow the effect to be detected, if it exists, with reasonable probability. The size requirement of the population can be estimated by power calculations.[7] In the following we present another simple but illustrative method. The reasoning is a slight modification of that presented by Pochin.[9] Let us consider a population with

the following characteristics:

X = number of persons
p = natural cancer risk per year
y = follow-up period (years)
D = radiation dose (mean value)
k = radiogenic cancer incidence per unit dose during the follow-up period.

The minimum latency time, if relevant, can be subtracted from y. The parameter p is a function of y; however, for our purposes it is sufficient to know the value of the natural cancer risk, py, during the study period. The total number of observed cases will be

$$Xpy + XkD. \tag{1}$$

If the radiation effect is considered to be detectable when the number of excess cases is double as compared with the variability of the expected number, then

$$XkD = 2\sqrt{Xpy}, \tag{2}$$

and consequently,

$$X = \frac{4py}{k^2D^2} \tag{3}$$

From this equation we see, as is often stated, that if a radiogenic effect is just observed at 1 Gy, a population 100 times larger is needed at 0.1 Gy and a population 10,000 times larger at 10 mGy. Note that similar relationship holds also for k, the radiogenic cancer incidence. The plot of equation (3) for different values of p, the normal cancer incidence, is shown in Fig. 1. The family of curves is calculated for a dose D = 10 mGy and for a follow-up period y = 20 yr.

As an example the upper curve refers to a hypothetical follow-up study of radiation-induced breast cancer among middle-aged US women (cf. ref. 7). The curve shows that with the current risk estimates ($(2\text{-}20) \times 10^{-6}$ mGy^{-1}) the low-level radiation effect is only seen in a very large population of women (5×10^6 - 10^8). However, if an increased risk is detected after a low-dose exposure in a population of more reasonable size ($<10^5$ women) this may mean that among this population the expression rate of radiation-induced malignant transformation is high.

The lowest curve is a simulation of the leukaemia risk. We see that leukaemia induced by radiation is much easier to detect than most other types of cancer, because of the high "signal-to-noise" ratio (low natural incidence of leukaemia). In the "Smoky" study[3,11] 3224 men participated in military maneuvers during a nuclear test explosion; the mean dose to the entire cohort was 4.7 mGy and 9 leukaemia cases were observed, whereas only 3.5 were expected. This statistically significant finding is possible if the radiation-induced leukaemia risk is over 100×10^{-6} mGy^{-1} (Fig. 1 or eq. (3)). Of course the "Smoky" study, by itself, does not prove that development of the radiation-induced primary damage to clinical leukaemia has been more common among these men than, say, among A-

bomb survivors, but such a possibility is not readily excluded either.

Discussion

The quantitative risk values extrapolated from high radiation doses vary greatly, depending on which kind of dose-response curve is assumed. The linear model is the one most commonly used, but the quadratic and linear-quadratic models also have their advocates. Further complications are introduced by the notion that the risk for radiation-induced cancer does not depend on dose only: biological variables - such as age, sex, genetic susceptibility, and exposure to other environmental carcinogens, co-carcinogens, promoters, etc. - may drastically modify the expression of the primary damage.

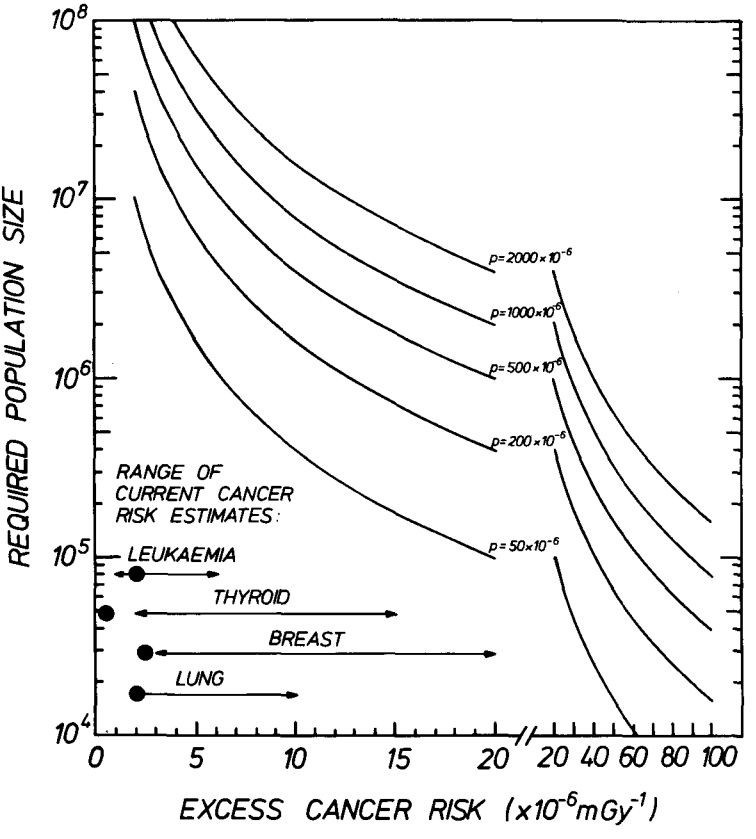

Fig. 1. Required population sizes in epidemiological studies as a function of excess cancer risk. The family of curves is calculated from eq. (3) with a radiation dose of 10 mGy and a follow-up period of 20 yr. The parameter p is the natural cancer incidence (see text). The black circles refer to the ICRP risk estimates;[5] the range of risk values is given by Pochin.[10] The curves may be used at all doses by properly selecting the ordinate; e.g. at 30 mGy the values quoted on the Y axis should be reduced by a factor of c. 10.

In conclusion, we suggest that the current risk estimates at low doses should be carefully reconsidered in the light of all epidemiological studies. It is not really justified to disregard one set of studies merely because the results are at variance with another set of data.

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