Reprinted from NEW YORK STATE JOURNAL OF MEDICINE, Vol. 80, No. 1, January 1980.

Cancer Effects of Low-Level Radiation

Theoretic considerations in competing causes of death

A. M. STEWART, M.D.
Edgbaston, Birmingham, England

From the Regional Cancer Registry, University of Birmingham

Studies of delayed effects of radiation are reviewed. Surveys with negative findings for small-dose effects have usually relied on extrapolations from large-dose effects and ignored two causes of nonrecognition of cancers in these situations: latent period deaths due to noncancer effects of the radiation, and latent period deaths due to the conditions which necessitated the exposures. Surveys with positive findings for low-level radiation suggest that the end results of such doses, delivered at a slow rate, may be very different from the end result of much larger doses delivered at a fast rate and that the difference is related to cell death effects of the radiation.

Ionizing radiations are powerful carcinogens, and, provided the age and species of the recipients are held constant, there is probably a middle range of radiation doses where cancer mortality effects are directly proportional to the dose. Nevertheless, in spite of radiation dose effects having been intensively studied by scientists from two disciplines, radiobiology and epidemiology, there is still uncertainty about whether or not to expect any cancer-induction effects from x-ray examinations or the doses encountered by workers in certain industries. According to one school of thought there is no danger at these low dose levels, a concept known as the safety threshold or nonlinear hypothesis. However, there is a rival school which believes that the cancer induction effects of radiation remain directly proportional to the dose however small, this concept known as the no safety threshold or linear hypothesis.

The two theories are mutually exclusive since one, the linear hypothesis or no safety threshold, would allow a single nonlethal mutation to initiate a cancer process, and the other, the nonlinear hypothesis or safety threshold, would require a different mechanism which is compatible with cancer induction's being the result of a particular sequence of cell changes. Meanwhile, in relation to the cancer effects of low-level radiation, radiobiologists have had consistently negative findings, and epidemiologists are still making contradictory claims. One of the surveys with positive findings may have ascribed to radiation the effects of other carcinogens,[1] and another may have placed too much reliance on retrospective data.[2] However, there is no proof that this is so, and we are clearly dealing with a situation in which there is more scope for false negative than false positive findings.

Neither in animals nor man can the origins of cancers be deduced from their clinical or pathologic manifestations. Therefore, even radiobiologists, who are free to experiment with the situation, have been forced to look for causal associations between radiation exposures and subsequent events; to use as indices of cancer induction either cancer mortality rates or prevalence; and to accept the fact that there will only be recognition of radiogenic and spontaneous cancers at a group level. There have been two approaches to the problem of small-dose effects: follow-up studies of human or animal populations exposed to uniform or variable doses, that is, prospective surveys; and case history studies of cancer patients, or retrospective surveys. Since intervals between cancer induction and diagnosis or death are of uncertain duration, both approaches require recognition and control of numerous factors related to cancer prevalence and mortality rates.

In planned studies the two groups of cancers which are otherwise indistinguishable, spontaneous and radiogenic, necessarily have different age distributions since, by definition, one consists of cases initiated at the time of the exposure and the other by different initiations. This is important for several reasons, including the possibility that cancers have sufficiently long latent periods for competing causes of death to be significant and even important statistical factors, and the possibility that some disturbance of general health, that is, changed reactions to diseases in general, occurred before a cancer developed to the point of being clinically recognizable.

The risk of dying from all causes is a function of infection susceptibility which is negatively correlated with age during the period of growth and development, that is, between conception and puberty, and positively correlated with age thereafter. Therefore, even on the assumption of no deterioration in health before a cancer is diagnosed, the proportion of both unrecognized and recognized cancer inductions, due to competing causes of death, would be different for spontaneous and radiogenic cases. Furthermore, the differences between the two groups would be con-

stantly changing since they would depend on several factors, including exposure, age, duration of the follow-up, the prevalence of other causes of death before and after radiologic exposure, and the intensity of the exposures.

The last factor is important and has often been overlooked by research workers whose estimates of small-dose effects were based on extrapolations from large doses. Cancers are far from being the only injurious effects of radiation, and we can be reasonably certain that all cell-damage effects are directly proportional to the dose. Therefore, extrapolations from high doses could be dangerous unless one allows for the possibilities that the proportion of unrecognized cancer inductions due to competing causes of death could be positively correlated with the radiation dose, different for radiogenic and spontaneous cases due to age differences, and different for internal and external radiation due to the different properties of alpha and gamma rays.

The cancers most likely to have changed reactions to other diseases before they are clinically recognizable are cancers of lymphatic and hemopoetic tissues, that is, RES (reticuloendothelial system) neoplasms. In one half of these cases there is no question of a painful lump being detected at a relatively early stage of the disease, and in all of them there is direct involvement of the immune system and a possibility of total loss of immunologic competence within a few weeks of confirmation of the diagnosis. Since an important component of the RES, bone marrow, heads the list of tissues which are exceptionally sensitive to the cancer-induction effects of radiation,[3] even a small increase in infection sensitivity during the latent phase of a bone marrow cancer such as myeloid leukemia or myelomatosis, would allow competing causes of death to have a selective harmful effect on the incidence and type of radiogenic cancers.

Finally both infections and cancers are under the control of the immune system. Therefore, it is possible that cancer sensitivity bears a similar relation to age as sensitivity to infection and is greater at the beginning than at the end of fetal life and prepuberty. An important cause of early death is a difficult delivery, and the usual time for x-raying pregnant women is toward the end of the gestation period. Therefore, in studies of the cancer effects of these in utero x-ray exposures allowance should be made for the following possibilities: (1) more cancer inductions during the first compared with the incidence in the second half of fetal life and different clinical forms of radiogenic cases between the earlier and the later initiations; and (2) more unrecognized cancer inductions following difficult than easy deliveries and more involvement of spontaneous than radiogenic cases in these early deaths.

Thus far, prospective surveys with negative findings for low-level radiation have been the sole source of guidelines for radiation protection purposes.[4,5] Risk estimates in support of these guidelines, usually in the form of maximal permissible doses, have accepted that the cancer effects of radiation are directly proportional to the dose. Therefore, are they exaggerating the risks with the safety threshold hypothesis, or are they understating the risks with rejection of a safety threshold?

Linear hypothesis (no safety threshold)

Surveys with positive findings for the hazard of low-level radiation have not relied on extrapolations from high doses. Since this is a constant feature of animal experiments, the main support for the linear hypothesis has come from (1) a follow-up of A-bomb survivors exposed to less than 10 rads, that is, the Japanese data; (2) several studies of the cancer effects of obstetric radiography, that is, fetal irradiation; and (3) a study of radiation doses of workers in the nuclear industry, known as the Hanford data.

Japanese data. For two groups of A-bomb survivors, at Hiroshima and Nagasaki, who were probably exposed to less than 10 rads in August, 1945, leukemia mortality rates during a 22-year period from October, 1950, to December, 1972, were increased by a significant amount compared with unexposed Japanese national rates.[6] The increase was greater for Hiroshima, 0.88 expected and 1.48 observed, than Nagasaki, 1.11 expected and 1.78 observed, but both differences were statistically significant.

Fetal irradiation. The most consistent findings for cancer effects of low-level radiation have come from case history studies of children who died from cancers before 10 years of age and who were x-rayed in utero for obstetric reasons.[2,7,8] The retrospective surveys have always shown higher exposure rates for these children than healthy controls, but an equivalent series of prospective surveys, that is, follow-up studies of in utero exposures, has yielded less consistent positive findings, even when the postexposure period was as long as the longest predeath period in the retrospective surveys.

There have been only three occasions when all the children in a prospective survey were followed for 10 years.[9–11] In two of the surveys, the source of the radiation was an x-ray examination. These exposures, which showed the usual bias in favor of third-trimester x-rays, had two groups of children, one with low rates of general mortality, whites in the United States, and one with high mortality rates, blacks in the United States. On the third occasion the children were A-bomb survivors who were exposed to a wide range of doses at different times between conception and birth and a grossly abnormal environment for at least five years after birth. For blacks in the United States and A-bomb survivors there was no evidence of any cancer effects from the in utero exposures, but for the two groups of whites in the United States there was definite evidence of such an effect.

For many years the positive findings for fetal irradiation were ascribed either to biased data sources or to the reasons requiring the x-rays.[5] Neither reason was likely, but both remained in circulation in the literature until the original retrospective survey[2] was in a position to include in a series of Mantel-Haneszel analyses, all factors suspected of having associations either with the exposures or the cancers.[12–15]

Each analysis took the form of a rigidly controlled test of a null hypothesis, and the series as a whole led to the following conclusions. The association between fetal irradiation and cancer was a direct one and was stronger for multiple than single exposures, and much stronger for near-conception than near-birth exposures. For a rare group of cancers with fetal manifestations, for example, teratomas, the cancers were the reason why the mothers were x-rayed, but otherwise the association was stronger for routine x-ray studies with normal findings than for special x-ray studies with abnormal findings. Yet "obstetric disproportion" as an x-ray finding, which has exceptionally strong associations with difficult deliveries, actually showed a negative correlation with childhood cancers.

Hanford data. Support for the linear hypothesis has come from a branch of the nuclear industry which has been kept under continuous surveillance since 1944.[1,16] It was originally intended to compare actual with expected cancer deaths by a method which is well known to cancer epidemiologists, but is slow to recognize small differences between observed and expected numbers of cancer deaths, determined by the SMR (standardized mortality ratio) method. However, the records included annual radiation doses of badge-monitored workers. Therefore, it was possible to make a forecast of mortality trends by comparing the radiation doses of workers who had died from stated causes.

According to these forecasts, cancer risks for workers in the nuclear industry are directly proportional to the dose and are related to age. At present, the showing is that cancers most likely to be caused by radiation are bone marrow, pancreas, and lung, but this could be a temporary phenomenon due to the fact that other cancers have longer latent periods.

Nonlinear hypothesis (safety threshold)

Quite apart from surveys with negative findings for fetal irradiation, there are many observations which favor the safety threshold model of radiation carcinogenesis. Most of the evidence comes from animal experiments, but the Japanese survey of A-bomb survivors has been quoted in this context as well as spondylitic data, that is, a survey of patients with ankylosing spondylitis who were given therapeutic doses of radiation with temporary relief of pain.

Japanese data. The ratio of observed to expected cancer deaths has always been lower in Nagasaki than in Hiroshima, but the proportion of acute leukemias has always been biased in the opposite direction.[4] These differences are supposed to be due to the different neutron content of the two bombs, but they could equally well be due to different concentrations of radioactive dust in the two situations.

The Hiroshima bomb fell on a flat plain and caused more injuries than the Nagasaki bomb, which fell in deep valley. Therefore, the hills must have offered some protection against the blast. By the same token, there must have been more radioactive dust in the valley than the plain. Therefore, we should expect troubles due to ingestion or inhalation of "hot" particles, that is, beta emitters, to be much greater in Nagasaki than in Hiroshima. This aspect of the bombing receives no mention in ABCC (Atomic Bomb Casualty Commission) publications, but it is nevertheless true that bone-marrow effects of beta emitters include permanent loss of immunologic competence, due to myelofibrosis, as well as acute myeloid leukemia.

In both cities residual effects of the blast were still being felt in 1960. Therefore, although the ABCC study population was not assembled until October, 1950, there was ample opportunity for radiation-induced loss of immunologic competence, or delayed effects of unmeasured doses of internal radiation, to prevent recognition of other delayed effects.

Spondylitic data. In the survey of patients with ankylosing spondylitis, everyone received a tissue-destructive dose to the spinal bone marrow. Also, the more crippled the patient, the greater the probability of receiving more than one course of radiotherapy. Therefore, there were two dose-related reasons why the proportion of unrecognized cancers due to latent period deaths should be increased: loss of immunologic competence due to radiation-induced myelofibrosis and similar effects due to the disease-causing rigidity of the thoracic cage.

In relation to this survey, there has only been mention of factors which might have added to the cancer risks. For example, the possibility of a direct connection between ankylosing spondylitis and leukemia has been mentioned, as well as the possibility of the use of drugs with carcinogenic properties, and the possibility that a rigid chest might increase a smoker's risk of lung cancer.[4,17] But the possibility that any disease requiring exposure to tissue-destructive doses of radiation could make it difficult to arrive at a true estimate of the cancer effects of radiation has been completely overlooked. Such an effect would be strongly age-related, and so this could be the reason why risk estimates based on spondylitic patients show much less variation with age than ones based on workers in the nuclear industry. For Hanford workers, the risk of premature death was small even compared with all men of working age, reflecting the so-called "healthy worker effect," and this could be the reason why an SMR analysis of

Hanford data actually found evidence of radiation effects for two rare groups of cancer, myelomatosis and pancreas, even though the overall cancer death rate was well below the national average.[18]

Comment

The fact that radiation has immediate as well as delayed health effects means that even if each effect were directly proportional to the dose, this would not be true of the net effect. It also means that the higher the dose the smaller the net effect per unit dose. The "cell death" component of this difference is well known, but there is no comparable recognition of the fact that tissue destruction by radiation need not be obvious to have lifelong effects. This uncomfortable fact is due partly to the extreme sensitivity of bone marrow but also to the strong affinity between radioactive substances and the inner lining of bone, which is also the outer lining of bone marrow.

We have yet to prove that there has been, in A-bomb survivors, both cancellation of the cancer effects of measured doses of external radiation by bone marrow effects of unmeasured doses of internal radiation and heightening of the first effect by the second effect, by the addition of bone-marrow cancers. But we can be reasonably certain that, even in relation to nonradiogenic cancers, there are changed reactions to other diseases during periods of cancer latency. These changes are more typical of leukemia than solid tumors. But for all forms of cancer there is an appreciable risk of dying from the effects of the disease before it can be recognized, and this risk is much greater in infancy and old age than it is during the intervening period.

Therefore, in any study of the cancer mortality effects of radiation it is important, not only to allow for inevitable age differences between spontaneous and radiogenic cancers, but also to remember that there will always be four factors influencing the proportion of unrecognized cancer initiations: the intensity of the exposures, the exposure age, the length of the postexposure period, and the general mortality rate.

University of Birmingham
Edgbaston
Birmingham, England

References

1. Mancuso, T. F., Stewart, A., and Kneale, G.: Radiation exposures of Hanford workers dying from cancer and other causes, Health Physics **33:** 369 (Nov.) 1977.
2. Stewart, A., Webb, J., and Hewitt, D.: A survey of childhood malignancies, Brit. M. J. **1:** 1495 (1958).
3. Radiosensitivity and Spatial Distribution of Dose, Publication 14, The International Commission on Radiological Protection, Elmsford, New York, Pergamon Press, 1969.
4. The effects of Populations of Exposure to Low Levels of Ionizing Radiation, BIER (Biological Effects of Ionizing Radiation) report, Washington, D.C., National Research Council, 1972.
5. Review of NCRP Radiation Dose Limit for Embryo and Fetus in Occupationally Exposed Women, Report 53, Washington, D.C., National Council on Radiation Protection and Measurements, 1977.
6. Pochin, E. E.: Malignancies following low radiation exposures in man, Brit. J. Radiol. **49:** 577 (1976).
7. Ford, D. D., Paterson, J. C., and Treuting, W. L.: Fetal exposure to diagnostic x-rays, and leukemia and other malignant diseases in childhood, J. Nat. Cancer Inst. **22:** 1093 (1959).
8. Graham S., et al.: Epidemiological approaches to the study of cancer and other chronic diseases, in Preconception, Intrauterine and Postnatal Irradiation as Related to Leukaemia, monograph 19, National Cancer Institute, 1966, p. 347.
9. MacMahon, B., and Hutchinson, G. B.: Prenatal x-ray and childhood cancer: a review, Acta Unio internat. contra cancrum **20:** 1172 (1964).
10. Diamond E. L., Schmerler, H., and Lilienfeld, A. M.: The relationship of intra-uterine radiation to subsequent mortality and development of leukemia in children. A prospective study, Am. J. Epidemiol. **97:** 283 (1973).
11. Jablon, S., and Kato, H.: Childhood cancer in relation to prenatal exposure to atomic-bomb radiation, Lancet **2:** 1000 (1970).
12. Kneale, G. W., and Stewart, A. M.: Mantel-Haenszel analysis of Oxford data. I. Independent effects of several birth factors including fetal irradiation, J. Nat. Cancer Inst. **56:** 879 (1976).
13. Ibid.: II. Independent effects of fetal irradiation subfactors, ibid. **57:** 1009 (1976).
14. Idem: Age variation in the cancer risks from foetal irradiation, Brit. J. Cancer **35:** 501 (Oct.) 1977.
15. Idem: Pre-cancers and liability to other diseases, ibid. **37:** 448 (Mar.) 1978.
16. Kneale, G. W., Stewart, A. M., and Mancuso, T. F.: Reanalysis of data relating to the Hanford study of the cancer risk of radiation workers, IAEA-SM-224/5, Vienna Congress, March 13 to 17, 1978.
17. Brown, W. M., and Doll, R.: Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis, Brit. M. J. **2:** 1327 (1965).
18. Gilbert, E. S., and Marks, S.: Cancer mortality in Hanford workers, IAEA-SM-224/4, ibid.