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Comments and Critique

Radiation From Chernobyl and Risk of Childhood Leukaemia

REPORTS OF cancer associated with man-made sources of ionising radiation initially appeared at the turn of the century, but it wasn't until the 1950s that systematic epidemiological investigations, such as the follow-up study of the Japanese atomic bomb survivors, commenced in earnest. In the past 4 decades, a rapidly expanding body of epidemiological and radiobiological studies has established ionising radiation as perhaps the best understood human carcinogen. Uncertainties remain, however, in our knowledge of radiation-related cancer, including the most appropriate methods for quantifying dose to tissues, extrapolating from moderate or high to low-dose exposures, from brief to long-term exposures, and from one population or time period to others. The possible interaction between ionising radiation and other carcinogenic agents is also poorly understood. These uncertainties were underscored following the Chernobyl nuclear power plant accident in April 1986, which released substantial amounts of radioactive material. Depending upon the assumptions used to predict the range of possible incremental increases in radiation-induced cancer risk, estimates of lifetime excess cancer among the world's population varied appreciably from small numbers to many thousands. Whether any excesses can be detected, however, is the question at hand.

There are perhaps four distinct populations, distinguished by level of exposure resulting from the Chernobyl accident, that could be studied epidemiologically [1–4]. These include: the most highly exposed group of people, consisting of a few thousand plant operators, engineers, guards, construction workers, firemen and policemen, who were directly involved in the accident and received an average estimated dose of 200 cGy (200 rad); the hundreds of thousands of people sent to Chernobyl between 1986 and 1989 to clean up the contamination, whose allowable cumulative dose initially established at 25 cGy, though rapidly and progressively reduced, may have been substantially higher for an undetermined number of workers; the approximately 35 000 area residents evacuated from a 30-km zone surrounding Chernobyl who were estimated to have received an average of about 40 cGy (among a total of 115 000 persons residing in the 30-km zone who were evacuated); and the populations of other regions in the former Soviet Union (FSU), eastern European countries near the Ukraine, and other parts of Europe who received low-level exposures estimated to average 0.1 cGy (0.1 rad) or less. As a point of reference, the estimated average natural background radiation level, excluding radon, is 0.1 cGy/year.

As soon as the accident at Chernobyl became known, an internationally coordinated effort to measure radionuclide deposition was implemented [1, 2] and committees of experts were convened to assess the feasibility of studies of health effects in the Soviet Union, and in Eastern and Western Europe. There was international agreement that long-term follow-up should be considered for the workers involved in the accident (among whom 31 deaths had already occurred due to the acute effects of whole body radiation), those participating in the subsequent decontamination efforts, the population evacuated from the Chernobyl region, and perhaps the approximately 100 000 residents of districts in the southeastern region of Belarus that had received substantial contamination (ranging from 0.56 to 1.48 TBq/km^2). Because of the exceptionally low exposure levels (less than background radiation and medical X-ray exposure) outside the 30-km area surrounding Chernobyl and the heavily contaminated areas in Belarus, it was concluded that epidemiological investigations to assess cancer in adults, malformations in children, and national differences in childhood cancer among populations in Europe would not produce scientifically useful information [3–5].

Nevertheless, the widespread public concern led some committees to endorse a carefully planned incidence survey comparing childhood cancer occurrence pre- and post-Chernobyl in specifically designated regions with high- and low-level radionuclide deposition. It was further recommended that the investigation be restricted to areas with high-quality, well-established, population-based cancer registration. A multi-registry population-based investigation in Europe and in selected areas of the FSU was organised by the International Agency for Research on Cancer (IARC), an organisation uniquely qualified because of long-standing experience in compiling international standardised cancer incidence data [6–8].

In this issue of the *European Journal of Cancer*, Parkin and colleagues (p. 87–95) present initial data from the IARC-organised European Childhood Leukaemia–Lymphoma Incidence Study (ECLIS). This report should reassure the public that large populations of children, i.e. those most sensitive to the carcinogenic action of ionising radiation, are under surveillance. No major conclusions can be drawn at this time since the length of follow-up is too short for excess leukaemia to appear among the exposed children. A precise estimate of leukaemia among prenatally exposed children is not yet available pending completion of the planned birth cohort analysis.

The ECLIS investigators are to be commended for their balanced presentation. Although they recognise the potential role of their investigation in reducing public concern, they state clearly the study limitations. In particular, because of extremely low doses, "no excess (cancer) incidence should be detectable anywhere with the possible exception of Belarus". A further constraint of this and other ecological studies is that any changes in leukaemia rates in regions with greater radiation contamination cannot be ascribed with certainty to the accident-related exposure, although the comparison of pre- and post-Chernobyl

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rates within, rather than between, regions may minimise some, but not all, potential confounding.

In addition to the limitations noted, the absence of population-based cancer registries in some regions receiving the highest doses may reduce the power of this study to detect an excess. Power may be further reduced by the heterogeneity of accident-related radiation doses in some large geographical regions estimated as receiving a uniform dose level, discrepancies between the time interval used for exposure estimation and that used for incidence data collection, and absence of adjustment for co-factors or effect modifiers that may be important in the radiation–leukaemia relationship. In contrast with these potentially correctable problems, at present it is not possible to morphologically distinguish the accident-related leukaemia cases from the baseline incident cases.

Although participating registries had to meet specified eligibility criteria, the accuracy of incidence estimates will vary among the regions due to differences in completeness and diagnostic accuracy of registration. Estimates are also likely to be affected by the greatly intensified search for leukaemia cases subsequent to Chernobyl, resulting in increased medical surveillance and leukaemia case-reporting [9]. Improvements in data quality during the study period, as noted by Parkin *et al.* (Table 2, p. 90), may also affect incidence rate estimates. Another source of concern in evaluating accuracy of incidence rates are possible errors in population estimates that may result from inadequate adjustment for immigration or emigration between censuses. Substantial population movement is also likely in view of the dramatic political events in the FSU and Eastern Europe over the last several years. Accompanying changes in social structures, medical care and health screening programs, as well as increased concern about potential radiation effects, may also affect population estimates and cancer reporting in the regions receiving the highest levels of radiation exposure outside the 30-km zone. Such societal changes could influence incidence estimates or produce spuriously high or erroneously low correlations between incidence rates and radionuclide dose in the affected study areas and, therefore, should be carefully considered.

In the planned birth cohort analyses, it may be difficult to assign prenatal exposure levels since place of birth is unknown for an unspecified proportion of children. The extent of possible exposure misclassification that may result from incorrect assumptions used for missing information could be difficult to estimate. As noted, the discrepancy between a subject's (or pregnant woman's) place of residence at the time of the accident and at the time of diagnosis will increase as the study interval lengthens. Parkin *et al.* suggest, however, that the likelihood of meaningful misclassification by dose is small because substantial cross-boundary movement is unlikely within the large geographical units under consideration. This conclusion seems overly optimistic in light of the major upheavals in Eastern Europe and the FSU during the past few years.

It would seem reasonable to focus surveillance efforts on childhood leukaemia since this neoplasm has been linked with extremely low-dose radiation (1–10 cGy from prenatal X-rays), and is characterised by a short latency period and a stronger association with ionising radiation than other cancers. All newly diagnosed childhood lymphoma cases in the study areas are also to be reported as part of the ECLIS study so that any leukaemia cases misclassified as lymphomas will also be included. The addition of lymphoma cases to the ECLIS study may be unlikely to improve the accuracy of the leukaemia incidence estimates, unless the specific leukaemia cases that have been mis-classified are separately identified. This would require central histopathological review of all lymphoma cases, and is not included in the methods section of the present paper.

Although of limited value for assessing any excess childhood leukaemia resulting from increased radiation exposure following the Chernobyl accident, the ECLIS study, as one of the largest international multi-registry incidence studies to date, may contribute in a broader sense to our understanding of the most common childhood neoplasm. The data are collected in a standardised fashion by registries generally established by 1980 or earlier. Data quality indicators are reported so that differences among the registries can be critically evaluated. To provide a data base for a more comprehensive evaluation of childhood leukaemia, it would be important to aim for close to 100% case ascertainment and reporting of cases within as short a period after diagnosis as possible. The resultant data could allow the investigators to accurately determine the level of variation in incidence among the reporting areas, and then explore possible reasons for the differences observed.

It may also be possible, at least in some regions, to expand the diagnosis-related data collected by the registry to include state-of-the-art morphological, cytogenetic, immunophenotypic and other characterisations of the leukaemia cases. It might then be possible to estimate incidence of biologically defined subgroups [10]. Another possible objective would be to assess possible aetiological differences among the biologically-defined subgroups, although a very large population base would be required given the rarity of childhood leukaemia.

The present IARC study may provide an opportunity to supplement our knowledge of the relationship of all types of environmental ionising radiation exposure with childhood leukaemia. Characterisation of region-specific measurement information on natural background gamma radiation and radon levels, as well as prevalence of diagnostic X-ray exposure among pregnant women and children, might be a useful addition to the ongoing measurements of radionuclide levels from Chernobyl. In this way, the accident-related exposures could be assessed in the context of natural background and medically-related exposures to ionising radiation. It may well be that estimated exposures from natural background radiation and medical X-rays greatly exceed the estimated exposure from Chernobyl.

Finally, the issue of public concern will undoubtedly continue to be an important influence. Hopefully, future reports by the ECLIS investigators will continue to include clear explanations regarding the scientific information this investigation will be able to provide. If the proposed 5-year follow-up shows a positive correlation, the ECLIS group could discuss the meaning of such a finding, along with possible alternative explanations and the many limitations of the ecological study methodology. If data are available, the investigators might wish to provide estimates of the number of cases thought to be related to radiation from Chernobyl, and to natural background and medical X-ray exposures given current estimates of radiation risk, and to examine the influence of the latter exposures as possible confounders of accident-related leukaemia occurrence. Should no correlation be found between childhood leukaemia or lymphoma and estimated radiation doses from Chernobyl, it could be helpful if the investigators were to discuss the implications of negative results.

The ECLIS investigation represents a landmark in collaborative epidemiological studies. The investigators are to be congratulated for their remarkable achievement in bringing together

scientists from politically and geographically diverse nations. If broadened in scope, this project has the opportunity to clarify and elucidate additional determinants of leukaemia.

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Anticancer Drug Screening and Discovery in the 1990s: A European Perspective

G. Schwartsmann and P. Workman

INTRODUCTION: THE NEED FOR CHANGE

ALTHOUGH ANTICANCER drug discovery efforts over the past 4 decades have resulted in the curability of some forms of disseminated malignancies, such as acute childhood leukaemias, Hodgkin's disease and germ cell tumours, the overall results of cytotoxic therapy in the most frequent solid tumours of the adult, particularly in the advanced metastatic stage, have remained far from satisfactory [1]. The lack of success in identifying new active agents against those common cancers with the most significant impact on the mortality rate generated a great deal of pessimism amongst drug screeners and clinicians in the 1980s [2–4]. Contrast this with the remarks of Nobel prizewinner and successful drug hunter Sir James Black on the opening of the Cancer Research Campaign Beatson Laboratories, Glasgow in April 1991: "There has never been a time like this for cancer research. There is a feeling of irrepressible optimism among scientists." These comments should apply no less to the development of new anticancer drugs than they do the extraordinary advances in our understanding of the molecular basis of changes which take place when a normal cell becomes a cancer cell. We shall argue here that the understandable pessimism referred to earlier is in fact entirely inappropriate [5]. Several new agents are showing impressive early clinical results despite acting on conventional drug targets, and perhaps more importantly, a host of more mechanistically innovative molecules are emerging which will exploit the various products of cancer genes.

Up to now, the identification of active agents against human cancers has relied essentially upon the following strategies: (1) random screening of natural and synthetic products in experimental tumours; (2) rational development of new compounds on the basis of observed biochemical properties of tumour vs. normal cells; (3) synthesis of analogues of known agents, usually seeking to eliminate an undesirable feature such as an unwanted side-effect or to incorporate an advantageous property such as broader spectrum of action or maintenance of activity in resistant tumours; and (4) serendipitous observation [4, 6, 7]. In practice, a combination of these approaches is often used.

In this review, we will take a critical look at the various approaches to new drug discovery in the 1990s and beyond. Unless we are extremely lucky, the new anticancer agents we

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