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Overview

The Chernobyl Accident—An Epidemiological Perspective

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Abstract

Twenty-five years have passed since radioactive releases from the Chernobyl nuclear accident led to the exposure of millions of people in Europe. Studies of affected populations have provided important new data on the links between radiation and cancer—particularly the risk of thyroid tumours from exposure to iodine isotopes—that are important not only for a fuller scientific understanding of radiation effects, but also for radiation protection. It is now well documented that children and adolescents exposed to radioiodines from Chernobyl fallout have a sizeable dose-related increase in thyroid cancer, with the risk greatest in those youngest at exposure and with a suggestion that deficiency in stable iodine may increase the risk. Data on thyroid cancer risks to other age groups are somewhat less definitive. In addition, there have been reported increases in incidence and mortality from non-thyroid cancers and non-cancer end points. Although some studies are difficult to interpret because of methodological limitations, recent investigations of Chernobyl clean-up workers ('liquidators') have provided evidence of increased risks of leukaemia and other haematological malignancies and of cataracts, and suggestions of an increase in the risk of cardiovascular diseases, following low doses and low dose rates of radiation. Further careful follow-up of these populations, including the establishment and long-term support of life-span study cohorts, could provide additional important information for the quantification of radiation risks and the protection of persons exposed to low doses of radiation.

Key words: Cancer; cataracts; cardiovascular diseases; Chernobyl accident; radiation; thyroid cancer

Statement of Search Strategies Used and Sources of Information

This overview is based on a detailed review of international peer-reviewed literature published since the 2006 Chernobyl Forum Review [1], found using PubMed, Medline and ISI, as well as key papers published before that, and publications in press based on international collaborations in which the authors participated.

Introduction

A number of studies of the health effects of radiation from the Chernobyl accident have been conducted in the last 25 years, mostly in the three most-affected states of Belarus, the Russian Federation and Ukraine [1,2].

These studies have provided very important new information on links between radiation and cancer that have ramifications for radiation protection, particularly in relation to the risk of thyroid tumours from exposure to iodine isotopes. Recent studies among Chernobyl liquidators have also provided some evidence of increases in the risk of leukaemia and other haematological malignancies and of cataracts and suggestions of increases in the risk of cardiovascular diseases following low doses and low dose rates of radiation.

The current paper reviews the epidemiological evidence to date concerning cancer and non-cancer outcomes published in the peer-reviewed international literature and discusses the important information that further, well-structured studies of specific exposed populations may provide for the quantification of radiation risks and the protection of persons exposed to low doses of radiation.

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Cancer Effects

Thyroid Cancer

Radiation and thyroid cancer before the Chernobyl accident

Thyroid cancer, a rare malignancy of the endocrine system, was first linked to external radiation exposure in a 1969 study of atomic bomb survivors [3]. Although the incidence peaked 25 years after the bombings [4] and has declined over time, thyroid cancer risk continues to be significantly elevated in this cohort 60 years later [5]. Both the studies of atomic bomb survivors and of patients receiving external radiation therapy for a range of malignant and benign conditions show a linear dose–response relationship and a higher risk for those exposed at <10–15 years of age [6,7]. The excess relative risk (ERR) for thyroid cancer induced by external radiation is generally more elevated in females than males, and radiogenic thyroid cancer is predominantly of the papillary histologic type rather than follicular, medullary or anaplastic [8].

Before the Chernobyl accident, internal radiation was believed to have relatively low or no malignant potential based primarily on the results from studies of adults exposed to diagnostic or therapeutic doses of radioiodines [9–11]. Although scant information was available on treated children, the presumption of no adverse effects was often extended to this age group, in spite of the fact that childhood exposure to relatively low doses of external radiation was known to increase the risk of thyroid tumours.

Radiation and thyroid cancer after Chernobyl

The first years after the Chernobyl accident were notable for several striking epidemiological observations. First, significant increases in paediatric thyroid cancer were reported in the two countries that were most contaminated by releases of radioiodines from the damaged nuclear reactor – Ukraine, the site of the Chernobyl plant [12], and Belarus, directly to the north [13,14]. The increases in thyroid cancer were particularly pronounced among those youngest at the time of exposure (0–4 years of age) and no increases were observed among adults. Although cases were relatively few, the increases were very large compared with previous years and the excess incidence was detectable statistically as early as 3–4 years after the accident. Most cases came from Gomel, Belarus, the region most heavily exposed, suggesting that iodine-131 (I-131), the chief component of accident fallout [15] and an isotope rapidly absorbed by the thyroid gland, was the probable cause of post-Chernobyl thyroid cancer in children.

Apart from these epidemiological features, the early cases of paediatric thyroid cancer had distinctive clinical and pathological characteristics. They were described as poorly differentiated, aggressive tumours that were invasive and metastatic [16–19], in spite of which survival has been excellent [1]. Among post-Chernobyl cases, papillary thyroid cancer was the most common histological type and cases were more often of the solid/follicular subtype than the classic papillary type characterised by less aggressive clinical behaviour. In early post-Chernobyl thyroid cancers, there were many tumours with *RET/PTC 3* rearrangements, which have been associated with the solid variant of papillary thyroid cancer [20].

Childhood exposure. In the decade after the accident, several ecological studies (i.e. studies based on data for groups rather than individuals) found significantly elevated risks for thyroid cancer in children from the three most-affected countries (reviewed in [1]). Two recent studies, one in Ukraine [21] and another in Belarus and Ukraine [22], have reported ERR/Gy of 8.0 (95% confidence interval: 4.6, 15) and 19 (95% confidence interval: 11, 27), respectively. An ecological study in the Bryansk region of Russia [23] provided the initial data—based on a small number of thyroid cancer cases—indicating that iodine deficiency and radiation dose from Chernobyl fallout acted jointly, with a two-fold higher ERR observed in areas of severe iodine deficiency compared with iodine-sufficient areas, as indicated by urinary iodine excretion levels.

The first analytical study of thyroid cancer and Chernobyl fallout [24], based on 107 young thyroid cancer patients from Belarus and two matched control groups, estimated an odds ratio for thyroid cancer among those exposed to mean settlement-based thyroid doses ≥1.0 Gy that was five-fold higher compared with those with estimated doses of <0.3 Gy. Subsequently, a smaller study in Russia of individuals 19 years or younger at the time of exposure (26 cases and 52 matched controls) with thyroid I-131 doses estimated for each subject from a semi-empirical model, reported a significantly increased risk of similar magnitude (odds ratio/Gy = 5.2) [25]. A large case–control study of Belarusian and Russian children younger than 15 years at the time of the accident (276 cases, mostly from Belarus, and 1300 matched controls) found an ERR/Gy of 5.6 among subjects with estimated doses of less than 1 Gy [26]. More recently, results of cancer prevalence analyses have been reported from two parallel cohort studies involving biennial thyroid screening examinations of about 25 000 exposed young people in northern Ukraine and Belarus 10–15 years after the accident [27,28]. Both studies—collaborations with the US National Cancer Institute—involved in-depth clinical examinations of the thyroid gland. The serial screenings, including palpation, ultrasound and measurement of thyroid hormones and antibodies, were standardised and given to all participants, regardless of dose, together with a series of structured interviews. The nature of the design obviated any effect of differential screening intensity and all cancer cases detected at examination were independently confirmed by international panels of experts. Individual estimates of I-131 were systematically developed based on thyroid scans carried out on all cohort members within 2 months of the accident together with environmental transfer models and interview data on subjects' residential histories and consumption of contaminated foods. Concentrations of stable iodine were measured in urine at the time of screening.

Analysis of 45 prevalent cases from the first screening cycle in Ukraine (1998–2000) showed a strong linear dose–response relationship between I-131 and thyroid cancer,

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with an excess odds ratio per Gray (EOR/Gy) of 5.25 (95% confidence interval: 1.7, 27.5), as well as suggestive trends in the expected direction with gender (female excess) and age at exposure (highest risk at youngest ages) [27]. Analysis of cancer prevalence in the Belarus cohort [28] showed that for subjects with thyroid doses <5 Gy ($n = 85$ cases), the dose response was linear, with risk being lower at higher doses. The EOR/Gy for the <5 Gy group was 2.15 (95% confidence interval: 0.81, 5.47), an estimate smaller in magnitude but statistically consistent with the estimate from the Ukrainian arm of the study and with estimates from previous case–control studies.

The prospective design and repeated measures of thyroid structure and function among exposed young subjects in the Ukrainian–American and Belarus–American studies offer the possibility of examining trends over time and buttressing predictions concerning the future level of risk. The results of an analysis of radiation-related incidence of thyroid cancer in the Ukrainian cohort are currently in press [29]. Sixty-five thyroid cancers were identified in the course of three examinations subsequent to the initial screening, representing about 73 000 person-years of observation. The dose response was consistent with linearity, as had been observed in the earlier ecological and case–control studies. The estimated ERR/Gy for incident thyroid cancer two decades after exposure was 1.91 (95% confidence interval: 0.43, 6.34). This is smaller than previously reported for prevalent thyroid cancer in this cohort (EOR/Gy = 5.25, 95% confidence interval: 1.7, 27.5) as well as for thyroid cancer risk in children exposed to external radiation (ERR/Gy from a pooled analysis of seven studies: 7.7; 95% confidence interval: 2.1, 28.7), but statistically the estimates are compatible. There was no evidence for a decrease in risk per Gy throughout the available observation period.

Continued follow-up, including the use of national cancer registries as a resource, will be needed to clarify whether the excess of papillary thyroid cancer in exposed children has plateaued or is beginning to decline, and whether radiation-related increases might start to appear in a different histological type.

In utero exposure. Because the thyroid is extremely sensitive to radioiodines in early childhood, due in part to the small size of the gland, one might also expect the fetus to be vulnerable. Moreover, the proliferative activity of fetal thyroid cells is high compared with that in children or adults [30]. To date, however, information about thyroid cancer risks associated with *in utero* exposure to Chernobyl fallout is very limited. In 2000, an ultrasound screening study of Belarusian school children living within 150 km of the Chernobyl plant [31] examined rates of thyroid cancer among those exposed prenatally ($n = 2409$) and those exposed before 3 years of age ($n = 9720$) and found higher rates in the postnatally exposed group compared with the *in utero* exposed (0.32%, $n = 31$ cases versus 0.09%, $n = 1$ case, respectively). A more recent (2003–2006) screening study of 2582 individuals in northern Ukraine who were *in utero* during the period of Chernobyl fallout [32] calculated the dose–response relationship for thyroid cancer using individually estimated fetal thyroid I-131 doses for each member of the cohort [33]. The EOR/Gy, based on seven prenatally exposed cases of thyroid cancer, was 11.9 ($P = 0.12$), substantially higher, but neither significant nor statistically different from the EOR/Gy of 3.24 estimated for a group of children exposed at 1–5 years of age ($n = 13$ cases, $P = 0.01$). The study in Ukraine had a longer period of follow-up than the earlier study in Belarus (about 20 years versus 14 years) and more accurate dosimetric data, but, although suggestive, it is by no means conclusive. Clearly the issue of *in utero* radiation exposure will require additional research to establish both its role in thyroid cancer aetiology and the relative radiosensitivity of the prenatal versus the postnatal thyroid gland.

Adult exposure. Data on thyroid cancer risk after adult exposure to external radiation are sparse. For treatment with radiotherapy, excess thyroid cancer risks have been reported for females [6,34], whereas a two-fold increased risk has been reported in X-ray operators compared with the general population [35]. In a recent analysis of atomic bomb survivors >20 years old at exposure [36], effects varied according to gender. Among females ($n = 241$ cases) the risk of thyroid cancer was elevated (ERR/Sv = 0.7, $P = 0.01$), although the magnitude of the radiation-related excess was much smaller than for children and decreased with time since exposure. Among males, the estimated dose–response relationship was negative (ERR/Sv = −0.25, $P = 0.31$).

There are also relatively few reports on adults exposed to I-131 from Chernobyl fallout. Two descriptive studies of thyroid cancer incidence in Ukraine and the Russian Federation, coordinated through the French–German Initiative for Chernobyl, found significant elevations during the period 1986–1999 in populations from the more contaminated areas [37,38]. Incidence rates for thyroid cancer in Belarus among individuals >19 years of age at the time of the accident have been reported to be higher than expected, beginning in 1991 through to the end of follow-up in 2002 [39]. However, when a study in the Bryansk region of Russia used individually estimated doses from a population registry rather than indicators like time trends or ground contamination, there was no association with thyroid cancer risk [37].

Among adults, those who participated in the post-accident clean-up sustained the highest radiation exposure after Chernobyl. Although several studies of this largely male group have been reported [40–42], findings have been inconsistent and the investigations have had methodological limitations, such as comparisons with rates in the general population for whom medical surveillance and reporting are less complete than for clean-up workers [43]. A dose–response analysis based on internal comparisons among Russian liquidators found no significant dose dependence with external radiation; indeed the central estimate was actually negative [40]. However, a study by the same investigators who focused on early liquidators who were potentially exposed to internal radiation as a result of the initial radioiodine releases from the reactor reported a significant increase in thyroid cancer risk [44]. In a recent International Agency for Research on Cancer case–control study of thyroid cancer among female as well as

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male clean-up workers from Belarus, Russia and the Baltic countries, individual external and internal radiation doses were reconstructed for 107 thyroid cancers and 423 matched controls [45]. The ERR/Gy for total dose was 0.38 (95% confidence interval: 0.10, 1.09) — higher than the ERR/Sv of 0.07 found for exposed adults among atomic bomb survivors. In addition to overall dose, the risk estimate was also statistically significant for the dose from I-131, owed primarily to ingestion of contaminated foods among workers commuting to work from homes in affected areas, although the risk estimates for external dose and internal dose were of similar magnitude. Both median dose and ERR/100 mGy were higher for females than for males.

The results to date from studies of thyroid cancer risk to adult residents of contaminated regions do not allow for ready conclusions and the important questions remain unanswered: Is there an excess risk of thyroid cancer in exposed adults? Does risk vary by gender? For the more heavily exposed Chernobyl liquidators, the data are more suggestive, but additional research will be needed to establish whether there is in fact a risk of thyroid cancer in this group and whether the risk is different for external and internal radiation.

Modifications of dose response

Age and time since exposure. From the available data, it seems that, as in the case of external radiation [2], thyroid cancer risk after I-131 exposure from Chernobyl decreases with increasing age at exposure. The data for some age groups are relatively sparse, however, and even for the more commonly studied population of exposed children and adolescents, the age at exposure trends are not always statistically significant. However, the excess post-Chernobyl thyroid cancers that are now occurring arise primarily in young adults who were exposed at young ages [46]. This, together with the more modest ERRs/Gy reported for exposed adults, suggests the age-at-exposure effect is probably real.

At present, long-term time trends, while of major importance in predicting the future level of risk, are not possible to determine with any degree of certainty. Both Belarus and Ukraine have reported continuing increases in thyroid cancer incidence for all ages and both genders. Although dose was not directly taken into account in either case, in Belarus greater increases were found in areas with higher exposure to Chernobyl fallout. The sole prospective cohort study, involving individual dose estimates and serial screening examinations of children and adolescents in Ukraine to 2007 [29], found no variation in radiation risk by time since exposure, a result compatible with studies of medical radiation in childhood in which thyroid cancer risk only began to decline 30 years after exposure [6,47].

Gender. Unlike age at exposure, the variation in radiation risk by gender in post-Chernobyl thyroid cancers has been inconsistent, with some studies finding a higher ERR in females than males [25,27,48] and others reporting the reverse pattern [21,22,28,49]. However, the accident-related increases have largely been in paediatric thyroid cancers where the gender ratio is much less marked than among adult cases. Because thyroid cancer occurs more often among females than males, studies using an excess absolute risk model, which is influenced by gender differences in background rates, are more consistent in finding females to be at higher risk.

Stable iodine status. Iodine is essential to the production of thyroid hormone and normal thyroid function, and seems to affect the occurrence and histological type of thyroid cancer [50]. Greater risk of developing thyroid cancer after radiation exposure in regions with iodine deficiency has been predicted [51]. Iodine-deficient thyroid glands have a higher uptake of radioiodines, leading to higher doses, and continuing effects of iodine deficiency may affect progression [52,53]. In spite of plausible reasons for postulating an interaction between iodine deficiency and radiation, as well as the fact that mild to moderate iodine deficiency is prevalent in Chernobyl-affected regions, only four studies to date have investigated the issue [23,26–28]. Although the studies differed in design and in the measure used to define stable iodine levels, all but one [27] reported a significant joint effect, with the exception possibly reflecting limited statistical power due to a relatively small number of cancer cases ($n = 45$) and little variability in the two indicators of iodine status examined (diffuse goiter and urinary iodine concentrations at the time of screening more than a decade after the accident). It is important that future studies assess the issue of effect modification with iodine status. Any final appraisal of the consequences of the Chernobyl accident for the thyroid cancer experience of those exposed to fallout will need to take account of the context with respect to background iodine levels in affected populations.

Leukaemia

Childhood and in utero exposures

Leukaemia was the first malignancy to be linked to radiation exposure among atomic bomb survivors [54] and has the highest radiation-related relative risk of all cancers, particularly after exposure in childhood. Increased risk has been observed in numerous epidemiological studies, with risks becoming apparent relatively soon after exposure (2–5 years) [4].

Several ecological studies have therefore examined the association between leukaemia risk and exposure to radiation from the Chernobyl accident in childhood, including the European Childhood Leukaemia-Lymphoma Study (ECLIS), a large-scale collaborative study based on existing cancer registries in Europe [55,56], and national incidence studies in Belarus [57,58] and Russia [59,60]. These are reviewed in detail in [1]. ECLIS found no evidence of a radiation-related increase in the incidence of leukaemia in Europe in the first 5 years after the accident. National studies do not, in general, provide evidence for an increase in the incidence of childhood leukaemia, although none was sufficiently sensitive to detect small changes in the incidence of such a rare disease and all are subject to methodological problems that may limit the interpretation of the findings. Several case–control studies of childhood leukaemia were also conducted in the

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most-contaminated regions of Belarus, the Russian Federation and Ukraine. An association between leukaemia risk and radiation dose was found in Ukraine, apparent (but not statistically significant) in Belarus, and not found in the Russian Federation [61–63]. The results, however, are difficult to interpret due to problems in the selection and comparability of controls in Ukraine.

An increase in infant leukaemia among those who were *in utero* at the time of the Chernobyl accident was reported by Petridou *et al.* [64] in an ecological study in Greece. The findings were based on small numbers of subjects (12 exposed cases and 31 unexposed cases). Several other ecological studies were conducted, including in the more contaminated areas of Belarus, with inconsistent results [1]. The issue of *in utero* exposure could not be addressed in the ECLIS study, as a number of cancer registries do not routinely collect exact date of birth.

Because of the large populations exposed *in utero* and in early childhood in the areas most contaminated by the Chernobyl accident, a careful study has the potential to provide important information for radiation protection about risks following low doses in this particularly vulnerable age group.

Adult exposure

Little new material on the risk of leukaemia after adult environmental exposure in the most-contaminated areas has been published since the 20th anniversary of Chernobyl. The results of studies available at that time are discussed in detail in [1] and were found to be inconclusive [65].

Since then, two case–control studies with detailed individual dose reconstruction have been published. One was nested within cohorts of liquidators from Belarus, the Russian Federation and the Baltic countries [66] and the other within the Ukrainian liquidator cohort [67]. Both studies used a jointly developed approach for individual dose reconstruction [68] based on detailed information collected by questionnaire on the place, time and conditions of work of the liquidators in the Chernobyl area. This information, which was reviewed and interpreted by expert dosimetrists familiar with the organisation of work and radiation protection measures after the accident, was linked with a large exposure rate database and sophisticated interpolation techniques that can be used to calculate exposure rates at places where liquidators lived and worked. Both studies found similar results, with ERRs of 4.8/Gy (90% confidence interval: nd − 33.1) for all leukaemia in the Baltic country/Belarus/Russian study and 3.44/Gy (95% confidence interval: 0.47–9.78) in the Ukrainian study. Both studies also found similar risk estimates for chronic lymphocytic leukaemia (CLL; a haematological malignancy type generally thought not to be related to radiation exposure) and for non-CLL leukaemia: the ERRs were, respectively, 4.7/Gy (90% confidence interval: nd − 76.1) for CLL and 5.0/Gy (90% confidence interval: <0–57.0) for non-CLL leukaemia in the Baltic country/Belarus/Russian study and 4.09 (95% confidence interval: <0–14.4) and 2.73 (95% confidence interval: <0–13.5), respectively, in the Ukrainian study. Although the ERRs/Gy for CLL are not statistically significantly elevated, this finding merits further study.

Other Cancers

Although ionising radiation has been shown to increase the risk of cancers at many sites, data from Chernobyl on cancers other than thyroid cancer are very sparse [2] and few studies have been published since the 20th anniversary of Chernobyl. The Chernobyl Forum report [1] reviewed these studies in detail. Although increases in the rates of a number of cancer types have been reported, these may be due to other factors, including improvements in registration, reporting and diagnosis [65]. However, because studies are few and have methodological limitations, it is premature to conclude that radiation from the Chernobyl accident did not have an effect on the incidence of these tumours. Furthermore, because of the long induction period for most cancers, it is too early to evaluate the full radiological impact of the accident. Continued monitoring of cancer trends in the most-affected countries, through the use and improvement of population-based cancer registries, is necessary.

Of particular interest among the increased cancer rates reported to date are those for breast cancer in the most-contaminated areas of Belarus and Ukraine. A detailed ecological epidemiological study, conducted to describe the spatial and temporal trends in breast cancer incidence in Belarus and Ukraine, reported a large increase in breast cancer incidence in all areas of Belarus and Ukraine, reflecting improvements in cancer diagnosis and registration. In addition to this, however, a significant increase in risk was also observed during the period 1997–2001, based on a relatively small number of cases, in the districts with the highest average dose levels compared with the least exposed districts, particularly among women who were youngest at the time of the accident, suggesting a possible radiation-induced risk [69].

Since then, a hospital-based case–control study of breast and ovarian cancer has been conducted in Belarus [70] investigating the effect of founder mutations in the BRCA1 gene and radiation exposure on the risk of breast cancer. The study included 1945 breast cancer cases, 201 ovarian cancer cases and 1019 controls. The subjects were stratified by region of origin, and classified as having lived in contaminated and non-contaminated areas. Patients in contaminated areas (Gomel, Mogilev) tended to have a lower median age at diagnosis (45 versus 50 years; $P = 0.00001$) and a higher proportion of familial history of breast cancer (odds ratio = 1.71, 95% confidence interval = 1.34–2.19) than those who lived in less contaminated regions. Carrier frequencies for the three tested founder BRCA1 mutations were not noticeably different between regions (5.2% versus 3.8%, odds ratio = 1.31, 95% confidence interval = 0.85–2.02, $P = 0.2$). Furthermore, although the effect of carrying a BRCA1 mutation on age at diagnosis was very pronounced in non-contaminated areas (median age 46 versus 50 years, $P < 0.00001$), it seemed to be less prominent in contaminated areas (42 versus 45 years, $P = 0.08$). Although the study participants in the contaminated areas were stratified by average level of dose based on the ecological classification in [69], no analysis of interaction between level of dose and founder mutation or family history was reported.

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This study adds to the growing evidence that women who carry mutations or variants in DNA repair and damage recognition genes may have an increased risk of breast cancer after exposure to ionising radiation even at low doses [71] and stresses the important role that further studies of breast cancer in the areas most contaminated by the Chernobyl accident may play in understanding radiation mechanisms and in improving radiation protection and public health.

Non-cancer Effects

A number of non-cancer end points have been reported in populations exposed to radiation from the Chernobyl accident. These are reviewed in [1]. Few studies are available in which individual dose estimates have been reconstructed and hence interpretation of the results is complex. Of particular note are studies of cardiovascular diseases and of cataracts among liquidators, which may have important implications for radiation protection.

Cardiovascular Diseases

Until now, cancer has been the main radiation-induced late effect considered for radiation protection after low dose protracted exposures. At high (therapeutic) doses, however, increases in the risk of other diseases, in particular cardiovascular diseases, have been shown consistently [72,73]. In recent years, evidence has also emerged suggesting that moderate doses of ionising radiation can contribute to excess cardiovascular disease risks [74,75]. In the absence of a proper understanding of the biological mechanism(s) that would lead to a radiation-related risk at low doses, it is not possible at present to draw conclusions about implications for the risk (if any) at low doses. If a risk exists, however, the impact in terms of radiation protection and public health would be important because of the already significant burden from diseases relating to the circulatory system.

Evidence for the risk for cardiovascular diseases associated with exposure from radiation emitted from the Chernobyl accident is at present limited. An analysis of non-cancer incidence and mortality rates in various groups registered in the Ukrainian State Chernobyl Registry—including workers, evacuees and residents of contaminated areas—found a decrease in the incidence of non-cancer diseases among recovery operations workers since 2000 [76]. However, the article lacks information about the methodology used in estimating disease rates and no information was available on doses to specific subjects.

A study in the Russian Federation focused on cardiovascular incidence among the cohort of Russian recovery operations workers. About 60 000 men with an average dose of 109 mGy were followed from 1986 to 2000. A statistically significant dose-related increased risk of ischaemic heart disease (ERR = 0.41, 95% confidence interval: 0.05, 0.78) and cerebrovascular diseases (ERR = 0.45, 95% confidence interval: 0.11, 0.80) was found [77]. However, the results should be interpreted with caution, as the study lacked information on other risk factors for these diseases (including smoking and other lifestyle factors).

Currently, there is great uncertainty regarding the effects of low to moderate doses on cardiovascular disease risks. The Chernobyl liquidator populations are particularly suitable to address this knowledge gap because of their large size and relatively higher dose levels (hence, higher statistical power) than other low dose populations.

Cataracts

The lens of the eye has long been considered a radiosensitive tissue [4,78], although induction of cataracts was thought to be deterministic in nature with a dose threshold of 0.5–2.0 Gy for acute exposure and of 5.0 Gy for protracted or fractionated exposure [79].

However, recent epidemiological studies have raised questions about the relationship between radiation and cataractogenesis [3]. A prospective cohort of 8607 Chernobyl Ukrainian liquidators was set up to review this issue. The study subjects were screened for cataracts 12 and 14 years after exposure. Beta-particle doses to the lens were estimated with an algorithm devised to take into account the nature and location of Chernobyl work, the time since the accident, and protective measures taken. The median lens dose in the cohort was 0.12 Gy. A statistically significant dose response was seen for stage 1 cataracts and, specifically, for posterior subcapsular cataracts [80]. When various cataract end points were analysed for dose thresholds, the confidence intervals all excluded values greater than 700 mGy, thus providing evidence of a risk for ‘detectable opacities’ from protracted exposures at doses substantially lower than those on which current radiation protection guidelines are based [81].

This cohort of liquidators with individual dose estimates provides a unique opportunity to assess the risk of radiation-induced cataracts, to estimate the magnitude of such a risk, to assess the rate of progression from early lens lesions to more advanced visual-impairing lesions, and to evaluate possible thresholds following doses to the lens within the low to medium range.

Discussion

Thyroid Cancer

Unquestionably, the most significant scientific lesson learned from Chernobyl is that exposure to internal radiation in childhood and adolescence causes an increase in papillary thyroid cancer. The suggestion from early descriptive studies has been confirmed in analytical studies with estimated doses and data on confounding and modifying variables. Although there are some differences, the magnitude of the excess thyroid cancer risks and the findings for effect modification by age at exposure and gender from this second wave of investigations are generally compatible with the data on external radiation. The shape of the dose–response curve is basically linear, with a suggestion of a downturn at higher

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doses. Twenty-five years after the accident, thyroid cancer risk in exposed young people continues to be significantly elevated.

As mentioned above, the duration and magnitude of post-Chernobyl thyroid cancer risk over time remain to be established. Although the excess risks reported to date from ecological, case–control and cohort studies of exposed young people are statistically compatible with one another, as well as with data on external radiation, central estimates of the ERR/Gy from some recent studies [28,29] appear to be somewhat smaller than those reported earlier [21,22,25–27]. Continued follow-up of the exposed population will be essential to an accurate description of the dynamics of the epidemic and prediction of future risk. Risks to those exposed as fetuses or adults remain uncertain due to limitations in the studies to date, both in the number and the quality. The possible effects of preconception exposure are also of interest, particularly now that those exposed early in life have reached reproductive ages.

Considerable attention has recently focused on how uncertainties in dosimetry may affect estimates of radiation-related thyroid cancer [82]. Only one published study to date has attempted to account for dose uncertainty [83]. Until such time as uncertainty in doses has been taken into account more systematically, reported risk estimates should be regarded as preliminary.

Monitoring Trends of Diseases

Although the main health effect of radiation from the Chernobyl accident observed to date is the dramatic increase in thyroid cancer among persons exposed at young ages, increases in the incidence of other types of cancer, in particular breast cancer, have also been reported, but have not been conclusively linked to radiation from the accident [1]. Continued surveillance of trends in cancer incidence, including thyroid cancer, is an important priority to evaluate the public health impact of the accident and should continue until the complete burden of Chernobyl-related disease has been fully characterised.

An area in which Chernobyl may provide particularly important information is the assessment of the risk of childhood leukaemia from *in utero* and early childhood exposures.

Further analytical studies of breast cancer risk in the most-contaminated areas, with analyses of gene–radiation interactions, are also of particular importance to further our understanding of radiation mechanisms and improve radiation protection practice both in the case of further accidents and for the protection of patients with medical exposures.

Chernobyl Life-span Studies

A careful assessment of the radiological effect of the accident would be greatly facilitated by the establishment and commitment to the long-term support of life-span studies, similar to that established in Hiroshima and Nagasaki after the bombings. This is one of the main conclusions and recommendations of the EU FP7-funded Agenda for Research on Chernobyl Health project (http://arch.iarc.fr/). The project, which was co-ordinated by the International Agency for Research on Cancer, assembled a multidisciplinary group of experts, from within and outside the most-affected states, with considerable experience in the follow-up of the health consequences of the accident. The group identified and prioritised the potential studies, assessed their feasibility, cost-effectiveness and likelihood of success, and provided a reasoned and comprehensive strategic research agenda for future research (http://arch.iarc.fr/documents/ARCH_SRA.pdf) [85]. Of particular importance are:

- Cohorts of liquidators. They currently exist in Russia, Belarus, Ukraine and the Baltic countries in the national Chernobyl registries. This group consists of about 600 000 individuals, of whom about 240 000 worked at the reactor site and the surrounding 30 km zone in 1986 and 1987, when doses were highest [65]. The average recorded dose for these liquidators was about 100 mSv, with few individual doses over 250 mSv. A number of nested case–control studies have been conducted successfully to evaluate the risk of thyroid cancer, leukaemia, and lymphoma associated with exposure during the clean-up of the accident [66,67]. This cohort would be invaluable in contributing new knowledge on the effects of low to moderate protracted doses on a number of health outcomes of interest (including cancer and non-cancer outcomes). It is a large cohort with a wide range of doses and as such is the population that will probably be most informative, with the greatest statistical power, for the evaluation of cancer and non-cancer effects.
- Cohorts of children with measured thyroid activity. As mentioned above, two general population cohorts have been established in Belarus (the BelAm cohort) and Ukraine (the UkrAm cohort) based on a sample of all individuals aged younger than 18 years who lived in contaminated regions and whose thyroid activity was measured within 2 months after the accident [1]. Sampling included all individuals with measured thyroid activity doses of 1 Gy or more and a random sample from two lower dose groups (0–0.29 and 3.39–0.99 Gy). The cohorts, which comprise about 12 000 subjects from Belarus and 13 000 from Ukraine who have been traced and have agreed to be screened, have been supported financially by the US National Cancer Institute and are administered jointly with the country concerned. Subjects were periodically screened for thyroid disease from about 1998 to 2007 and, as the results reported above indicate, have provided valuable information on the risk of thyroid cancer [28,29] as well as non-malignant thyroid disease risk [27,84]. These cohorts are a unique source of information, not only for the study of thyroid diseases, but also for a number of other outcomes for which active follow-up is needed in a well-defined population with individual dose estimates.

Conclusions

Twenty-five years have passed since the Chernobyl accident led to the exposure of millions of people in Europe. Studies of populations exposed have provided significant new information on radiation risks, particularly in relation to thyroid tumours following exposure to iodine isotopes. Recent studies among Chernobyl liquidators have also provided evidence of increases in the risk of leukaemia and other haematological malignancies and of cataracts, and suggestions of increases in the risk of cardiovascular diseases, following low doses and low dose rates of radiation.

Further careful follow-up of these populations, and the establishment and long-term support of life-span study cohorts, may continue to provide important information for the quantification of radiation risks and the protection of persons exposed to low doses of radiation.

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