Published in final edited form as:

Clin Oncol (R Coll Radiol). 2011 May ; 23(4): 251–260. doi:10.1016/j.clon.2011.01.510.

The Chernobyl accident — an epidemiological perspective

E. Cardis¹ and M. Hatch²

¹ Centre for Research in Environmental Epidemiology (CREAL), Municipal Institute of Medical Research (IMIM), CIBERESP, Barcelona, Spain

² Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Building EPS, MS 7238, Rockville, Maryland 20852, United States of America

Abstract

Twenty-five years have passed since radioactive releases from the Chernobyl nuclear accident led to 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 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 endpoints. 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 hematological malignancies and of cataracts, and suggestions of an increase in risk of cardiovascular diseases, following low doses and low dose rates of radiation.

Further careful follow-up of these populations, including 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.

© 2011 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

Corresponding author: Elisabeth Cardis, CREAL-Centre for Research in Environmental Epidemiology Parc de Recerca Biomèdica de Barcelona, Doctor Aiguader, 88, 08003 Barcelona, Tel. +34 932 147 312 | Fax +34 932 147 301, ecardis@creal.cat.

Searches

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.

Conflict of Interest

The authors have no conflict of interest to declare.

Elisabeth Cardis was involved in the IARC-led collaborative studies on the health effects of the Chernobyl accident in Belarus, Russia, Ukraine and Baltic countries and is member of the ARCH Core Group (<http://arch.iarc.fr/>).

Maureen Hatch has been involved in the NCI-led collaborative studies on the health effects of the Chernobyl accident in Belarus and Ukraine and is an adviser to ARCH.

Both were involved in the WHO evaluation of the health effects of the accident within the UN Chernobyl Forum (1).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 which 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.

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 (ABS) (3). Although 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 ABS 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 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).

Prior to Chernobyl, 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 tumors.

Radiation and thyroid cancer post-Chernobyl—The first years following the Chernobyl accident were notable for several striking epidemiologic observations. First, significant increases in pediatric 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 to previous years and the excess incidence was detectable statistically as early as 3–4 years post-accident. The majority of 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 likely cause of post-Chernobyl thyroid cancer in children.

Apart from these epidemiologic features, the early cases of pediatric thyroid cancer had distinctive clinical and pathologic characteristics. They were described as poorly differentiated, aggressive tumors that were invasive and metastatic (16–19), in spite of which survival has been excellent (1). Among post-Chernobyl cases, papillary thyroid cancer (PTC) was the most common histologic type and cases were more often of the solid/follicular subtype than the classic papillary type characterized by less aggressive clinical behavior. In early post-Chernobyl thyroid cancers, there were many tumors with *RET/PTC 3* rearrangements, which have been associated with the solid variant of papillary thyroid cancer (20).

1. Childhood exposure: In the decade following the accident, several ecologic studies (ie, studies based on data for groups rather than individuals) found significantly elevated risks for thyroid cancer in children from the three most affected countries (these are reviewed in (1)). Two recent studies, one in Ukraine (21) and another in Belarus and Ukraine (22), have reported Excess Relative Risks/Gray (ERR/Gy) of 8.0 (95% Confidence Interval (CI): 4.6, 15) and 19 (95% CI: 11, 27), respectively. An ecologic 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 (ID) and radiation dose from Chernobyl fallout acted jointly, with a twofold higher ERR observed in areas of severe ID compared with iodine sufficient areas as indicated by urinary iodine excretion levels.

The first analytic 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 (OR) for thyroid cancer among those exposed to mean settlement-based thyroid doses ≥ 1.0 Gy that was fivefold higher compared to 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 (OR/Gy=5.2) (25). A large case-control study of Belarusian and Russian children less than age 15 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 U.S. 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 standardized and administered to all participants, regardless of dose, along with a series of structured interviews. The nature of the design obviated any effect of differential screening intensity and all cancer cases detected at exam were independently confirmed by international panels of experts. Individual estimates of I-131 were systematically developed based on thyroid scans performed on all cohort members within two months of the accident along 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, with an EOR/Gy of 5.25 (95% CI 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% CI 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 ~73,000 person-years of observation. The dose-response was consistent with linearity, as had been observed in the earlier ecologic and case-control studies. The estimated ERR/Gy for incident thyroid cancer two decades following exposure was 1.91 (95% CI: 0.43, 6.34). This is smaller than what was previously reported for prevalent thyroid cancer in this cohort (EOR/Gy=5.25, 95% CI: 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% CI: 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 histologic type.

2. *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=2,409) and those exposed before three years of age (n=9,720) and found higher rates in the postnatally exposed group compared with the *in utero* exposed (0.32%, n=31 cases vs. 0.09%, n=1 case, respectively). A more recent (2003–2006) screening study of 2,582 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 (approximately 20 years vs. 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 etiology and the relative radiosensitivity of the prenatal vs. the postnatal thyroid gland.

3. Adult exposure: Data on thyroid cancer risk following adult exposure to external radiation are sparse. For treatment with radiotherapy, excess thyroid cancer risks have been reported for females (6;34), while a twofold increased risk has been reported in X-ray operators compared to 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 the end of follow-up in 2002 (39). However, a study in the Bryansk region of Russia using individually estimated doses from a population registry rather than indicators like time trends or ground contamination, found 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 methodologic 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 which 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 IARC (International Agency for Research on Cancer) case-control study of thyroid cancer among female as well as 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% CI: 0.10, 1.09)– higher than the ERR/Sv of 0.7 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, though the risk estimates for external dose and internal dose were of similar magnitude. Both median dose and $ERR/100mGy$ 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

1. Age and time since exposure: From the available data, it appears that, as in the case of external radiation (2), thyroid cancer risk following 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 likely to be 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 through 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 post-exposure (6;47).

2. 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 pediatric thyroid cancers where the sex ratio is much less marked than among adult cases. Since thyroid cancer occurs more often among females than males, studies using an excess absolute risk model (EAR) which is influenced by gender differences in background rates are more consistent in finding females to be at higher risk.

3. Stable iodine status: Iodine is essential to the production of thyroid hormone and normal thyroid function, and appears to affect the occurrence and histologic 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 ID may impact progression (52;53). In spite of plausible reasons for postulating an interaction between ID and radiation as well as the fact that mild- to moderate-ID 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.

Leukemia

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 following 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 five-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 most contaminated regions of Belarus, the Russian Federation and Ukraine. An association between leukaemia risk and radiation dose was found in Ukraine (61–63), apparent (but not statistically significant) in Belarus, and not found in the Russian Federation (62). Results however are difficult to interpret due to problems in the selection and comparability of controls in Ukraine.

An increase of infant leukaemia among those who were *in utero* at the time of Chernobyl accident was reported by Petridou et al. in an ecological study in Greece (64). 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, however, 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 risk of leukaemia following 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 liquidators 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% CI: n.d. – 33.1) for all leukaemia in the Baltic country/Belarus/Russian study and 3.44/Gy (95% CI: 0.47 - 9.78), respectively 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% CI: n.d. – 76.1) for CLL and 5.0/Gy (90% CI: <0 – 57.0) for non-CLL leukaemia in the Baltic country/Belarus/Russian study and 4.09 (95% CI: <0 – 14.4) and 2.73 (95% CI: <0 – 13.5), respectively, in the the Ukrainian study. Though 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 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 highest average dose levels compared to 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 was 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 vs. 50 years; $p = 0.00001$) and a higher proportion of familial history of breast cancer ($OR = 1.71$, 95% $CI = 1.34–2.19$) 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% vs. 3.8%, $OR = 1.31$, 95% $CI = 0.85–2.02$, $p = 0.2$). Furthermore, while the effect of carrying a BRCA1 mutation on age at diagnosis was very pronounced in non-contaminated areas (median age 46 vs. 50 years, $p < 0.00001$), it appeared to be less prominent in contaminated areas (42 vs. 45 years, $p = 0.08$). Though 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.

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 following exposure to ionizing 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 endpoints 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 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 following 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 ionizing 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 (USCR) — 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). The article lacks information about the methodology used in estimating disease rates, however, 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 ischemic heart disease (ERR= 0.41, 95% CI; 0.05–0.78) and cerebrovascular diseases (ERR= 0.45, 95% CI; 0.11–0.80) was found (77). Results should, however, be interpreted with caution as the study lacks 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), though 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).

Recent epidemiological studies, however, have raised questions about the relation between radiation in cataractogenesis (3). A prospective cohort of 8,607 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, 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 analyzed 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 risk, to assess the rate of progression from early lens lesion to more advanced visual-impairing lesions, and to evaluate possible threshold 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 analytic 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 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 ecologic, 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 number and 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.

Finally, as discussed in detail elsewhere in this issue, further research on clinical, histologic and molecular characteristics of future post-Chernobyl thyroid cancers is also needed.

Monitoring trends of diseases

Though 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 characterized.

An area in which Chernobyl may provide particularly important information is the assessment of 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 protection of patients with medical exposures.

Chernobyl life span studies

A careful assessment of the radiological impact 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 (ARCH) project (<http://arch.iarc.fr/>). ARCH, which was coordinated by the International Agency for Research on Cancer (IARC), 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). 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 approximately 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 is 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, leukemia, and lymphoma associated with exposure during clean up of the accident (84;85). 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 likely to 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 two 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 3.39–0.99Gy). 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 NCI and are administered jointly with the country concerned. Subjects were periodically screened for thyroid disease from approximately 1998–2007 and, as the results reported above indicate, have provided valuable information on risk of thyroid cancer (27–29) as well as non-malignant thyroid disease risk (86). 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 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.

Acknowledgments

This research was supported in part by the Intramural Research Program of the U.S. National Cancer Institute, NIH, DHHS.

The authors wish to acknowledge all the people in Europe – in particular in the most affected states of Belarus, Russia and Ukraine – as well as in Japan and North America who have worked tirelessly in the last 25 years to evaluate the health impact of the Chernobyl accident and to draw lessons from this catastrophe to improve the health of the affected populations, better understand radiation risks and improve the basis for radiological protection of populations. A special note is made of the invaluable contributions of the late Geoffrey Howe (Columbia University) and Elaine Ron (US National Cancer Institute).

Reference List

1. UN Chernobyl Forum. Health Effects of the Chernobyl Accident and Special Health Care Programmes. In: Bennett, B.; Repacholi, M.; Carr, Z., editors. World Health Organisation Report of the UN Chernobyl Forum expert group “Health” (EGH). Geneva: 2006.
2. United Nations (UN). Report to the General Assembly, Scientific Annexes C, D and E, UNSCEAR 2008 Report. Vol. II. New York, United Nations: 2011. Sources and Effects of Ionizing Radiation.
3. Wood JW, Tamagaki H, Neriishi S, Sato T, Scheldon WF, Archer PG, et al. Thyroid carcinoma in atomic bomb survivors Hiroshima and Nagasaki. *Am J Epidemiol*. 1969; 89(1):4–14. [PubMed: 5762817]
4. UNSCEAR. Effects. Vol. II. New York, United Nations: 2000. Sources and Effects of Ionizing Radiation.
5. Imaizumi M, Ashizawa K, Neriishi K, Akahoshi M, Nakashima E, Usa T, et al. Thyroid diseases in atomic bomb survivors exposed in utero. *J Clin Endocrinol Metab*. 2008; 93(5):1641–1648. [PubMed: 18319305]
6. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res*. 1995; 141(3):259–277. [PubMed: 7871153]
7. Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. *Radiat Res*. 1994; 137(2 Suppl):S17–S67. [PubMed: 8127952]
8. Hall, P.; Adami, HO. Thyroid cancer. In: Adami, HO.; Hunter, D.; Trichopoulos, D., editors. Textbook of Cancer Epidemiology. New York: Oxford University Press; 2002. p. 504–519.
9. Dickman PW, Holm LE, Lundell G, Boice JD Jr, Hall P. Thyroid cancer risk after thyroid examination with ¹³¹I: a population-based cohort study in Sweden. *Int J Cancer*. 2003; 106(4):580–587. [PubMed: 12845656]
10. Holm LE, Wiklund KE, Lundell GE, Bergman NA, Bjelkengren G, Cederquist ES, et al. Thyroid Cancer After Diagnostic Dose of Iodine-131: A Retrospective Cohort Study. *JNCI*. 1988; 80:1132–1138. [PubMed: 3411626]
11. Hall P, Berg G, Bjelkengren G, Boice JD Jr, Ericsson UB, Hallquist A, et al. Cancer mortality after iodine-131 therapy for hyperthyroidism. *Int J Cancer*. 1992; 50:886–890. [PubMed: 1555888]
12. Prisyazhiuk A, Pjatak OA, Buzanov VA, Reeves GK, Beral V. Cancer in the Ukraine, post-Chernobyl [letter]. *Lancet*. 1991; 338:1334–1335. [PubMed: 1682710]
13. Kazakov VS, Demidchik EP, Astakhova LN. Thyroid cancer after Chernobyl [letter]. *Nature*. 1992; 359:21. [PubMed: 1522879]

14. Baverstock K, Egloff B, Pinchera A, Ruchti C, Williams D. Thyroid cancer after Chernobyl. *Nature*. 1992; 359(6390):21–22. [PubMed: 1522880]
15. UNSCEAR. UNSCEAR 1988 Report. New York: United Nations Scientific Committee on the Effects of Atomic Radiation, United Nations; 1988. Sources and Effects of Ionizing Radiation.
16. Nagataki, S., editor. Thyroid cancer in children after the Chernobyl accident: clinical and epidemiological evaluation of 251 cases in the Republic of Belarus. Amsterdam: Elsevier Science, B.V.; 1994.
17. Tronko, ND.; Epstein, Y.; Oleinik, V. Thyroid gland in children after the Chernobyl accident (yesterday and today). In: Nagataki, S., editor. Nagasaki Symposium on Chernobyl: Update and Future. Amsterdam: Elsevier Science; 1994. p. 3–46.
18. Farahati J, Demidchik EP, Biko J, Reiners C. Inverse association between age at the time of radiation exposure and extent of disease in cases of radiation-induced childhood thyroid carcinoma in Belarus. *Cancer*. 2000; 88(6):1470–1476. [PubMed: 10717632]
19. Reiners C, Demidchik YE. Differentiated thyroid cancer in childhood: pathology, diagnosis, therapy. *Pediatr Endocrinol Rev*. 2003; 1 (Suppl 2):230–235. [PubMed: 16444163]
20. Thomas GA, Bunnell H, Cook HA, Williams ED, Nerovnya A, Cherstvoy ED, et al. High prevalence of RET/PTC rearrangements in Ukrainian and Belarussian post-Chernobyl thyroid papillary carcinomas: a strong correlation between RET/PTC3 and the solid-follicular variant. *J Clin Endocrinol Metab*. 1999; 84(11):4232–4238. [PubMed: 10566678]
21. Likhtarev I, Kovgan L, Vavilov S, Chepurny M, Ron E, Lubin J, et al. Post-Chornobyl thyroid cancer in Ukraine. Report 2: Risk anaysis. *Radiat Res*. 2006; 166(2):375–386. [PubMed: 16881739]
22. Jacob P, Bogdanova TI, Buglova E, Chepurniy M, Demidchik Y, Gavrilin Y, et al. Thyroid cancer risk in areas of Ukraine and Belarus affected by the chernobyl accident. *Radiat Res*. 2006; 165(1): 1–8. [PubMed: 16392956]
23. Shakhtarin VV, Tsyb AF, Stepanenko VF, Orlov MY, Kopecky KJ, Davis S. Iodine deficiency, radiation dose, and the risk of thyroid cancer among children and adolescents in the Bryansk region of Russia following the Chernobyl power station accident. *Int J Epidemiol*. 2003; 32(4): 584–591. [PubMed: 12913034]
24. Astakhova LN, Anspaugh LR, Beebe GW, Bouville A, Drozdovitch VV, Garber V, et al. Chernobyl-related thyroid cancer in children of Belarus: a case-control study. *Radiat Res*. 1998; 150(3):349–356. [PubMed: 9728663]
25. Davis S, Stepanenko V, Rivkind N, Kopecky KJ, Voilleque P, Shakhtarin V, et al. Risk of thyroid cancer in the Bryansk oblast of the Russian Federation after the Chernobyl power station accident. *Radiat Res*. 2004; 162(3):241–248. [PubMed: 15332999]
26. Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, et al. Risk of thyroid cancer after exposure to ¹³¹I in childhood. *J Natl Cancer Inst*. 2005; 97(10):724–732. [PubMed: 15900042]
27. Tronko MD, Howe GR, Bogdanova TI, Bouville AC, Epstein OV, Brill AB, et al. A cohort study of thyroid cancer and other thyroid diseases after the chornobyl accident: thyroid cancer in Ukraine detected during first screening. *J Natl Cancer Inst*. 2006; 98(13):897–903. [PubMed: 16818853]
28. Zablotska LB, Ron E, Rozhko AV, Hatch M, Polyanskaya ON, Brenner AV, et al. Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. *Br J Cancer*. 2010 Nov 23.
29. Brenner AV, Tronko MD, Hatch M, Bogdanova T, Oliynyk V, Lubin J. I-131 dose response for incident cancers in Ukraine related to the Chornobyl accident. *Environ Health Perspect*. In press.
30. Saad AG, Kumar S, Ron E, Lubin JH, Stanek J, Bove KE, et al. Proliferative activity of human thyroid cells in various age groups and its correlation with the risk of thyroid cancer after radiation exposure. *J Clin Endocrinol Metab*. 2006; 91(7):2672–2677. [PubMed: 16670159]
31. Shibata Y, Yamashita S, Masyakin VB, Panasyuk GD, Nagataki S. 15 years after Chernobyl: new evidence of thyroid cancer. *Lancet*. 2001; 358(9297):1965–1966. [PubMed: 11747925]
32. Hatch M, Brenner A, Bogdanova T, Derevyanko A, Kuptsova N, Likhtarev I, et al. A screening study of thyroid cancer and other thyroid diseases among individuals exposed in utero to

- iodine-131 from Chernobyl fallout. *J Clin Endocrinol Metab.* 2009; 94(3):899–906. [PubMed: 19106267]
33. Likhtarev I, Kovgan L, Chepurny M, Ivanova O, Boyko Z, Ratia G, et al. Estimation of the thyroid doses for Ukrainian children exposed in utero after the Chernobyl accident. *Health Phys.* In press.
 34. Boice JD Jr, Engholm G, Kleinerman RA, Blettner M, Stovall M, Lisco H, et al. Radiation Dose and Second Cancer Risk in Patients Treated for Cancer of the Cervix. *Radiat Res.* 1988; 116:3–55. [PubMed: 3186929]
 35. Carstensen JM, Wingren G, Hatschek T, Fredriksson M, Noorlind-Brage H, Axelsson O. Occupational risks of thyroid cancer: Data from the Swedish Cancer Environment Register, 1961–1979. *Am J Ind Med.* 1990; 18(5):535–540. [PubMed: 2244626]
 36. Richardson DB. Exposure to ionizing radiation in adulthood and thyroid cancer incidence. *Epidemiology.* 2009; 20(2):181–187. [PubMed: 19177023]
 37. Ivanov VK, Gorski AI, Maksoutov MA, Vlasov OK, Godko AM, Tsyb AF, et al. Thyroid cancer incidence among adolescents and adults in the Bryansk region of Russia following the Chernobyl accident. *Health Phys.* 2003; 84(1):46–60. [PubMed: 12498517]
 38. Prisyazhnyuk AE, Gristchenko V, Fedorenko Z, Gulak L, Fuzik M, Slipeniuk Y, et al. Twenty years after the Chernobyl accident: solid cancer incidence in various groups of the Ukrainian population. *Radiat Environ Biophys.* 2007; 46:43–51. [PubMed: 17279359]
 39. Kenigsberg, J.; Buglova, E. Health consequences. In: Smith, J.; Beresford, N., editors. *Chernobyl: Catastrophe and consequences.* New York: Springer-Verlag; 2005.
 40. Ivanov VK, Tsyb AF, Petrov AV, Maksoutov MA, Shilyaeva TP, Kochergina EV. Thyroid cancer incidence among liquidators of the Chernobyl accident. Absence of dependence of radiation risks on external radiation dose. *Radiat Environ Biophys.* 2002; 41(3):195–198. [PubMed: 12373328]
 41. Karaoglou, A.; Desmet, G.; Kelly, GN.; Menzel, HG., editors. *Chernobyl NPP accident consequences cleaning up participants in Ukraine - health status epidemiologic study - main results.* Brussels: European Commission; 1996.
 42. Okeanov, AE.; Ivanov, VC.; Cardis, E.; Rastoptchin, E.; Sobolev, A.; Lav, C., et al. Study of cancer risk among liquidators, Report of EU Experimental collaboration project 7: Epidemiologic Investigations including Dose Assessment and Dose Reconstruction. Vol. 95/002. Lyon: International Agency for Research on Cancer; 1995.
 43. Cardis, E.; Anspaugh, L.; Ivanov, VK.; Likhtarev, IA.; Mabuchi, K.; Okeanov, AE., et al. Summing up the Consequences of the Accident. Vienna: International Atomic Energy Agency; 1996. Estimated long term health effects of the Chernobyl accident. One Decade after Chernobyl; p. 241-279.
 44. Ivanov VK, Chekin SY, Kashcheev VV, Maksoutov MA, Tumanov KA. Risk of thyroid cancer among Chernobyl emergency workers of Russia. *Radiat Environ Biophys.* 2008; 47(4):463–467. [PubMed: 18551301]
 45. Kesminiene A, Evrard AS, Ivanov VK, Malakhova IV, Kurtinaitis J, Stengrevics A, et al. Risk of thyroid cancer among Chernobyl liquidators. *Radiat Res.* (submitted).
 46. Williams ED. Chernobyl and thyroid cancer. *J Surg Oncol.* 2006; 94(8):670–677. [PubMed: 17131413]
 47. Shore, R.; Xue, XN. Comparative thyroid cancer risk of childhood and adult radiation exposure and estimation of lifetime risk. In: Karaoglou, A.; Williams, ED., editors. *Radiation and thyroid cancer.* Singapore: World Scientific Publishing; 1999. p. 491-498.
 48. Heidenreich WF, Bogdanova TI, Jacob P, Biryukov AG, Tronko ND. Age and time patterns in thyroid cancer after the Chernobyl accidents in the Ukraine. *Radiat Res.* 2000; 154(6):731–732. [PubMed: 11187019]
 49. Buglova, E.; Demidchik, E.; Kenigsberg, J.; Golovneva, A. Thyroid cancer in Belarus after the Chernobyl accident: incidence, prognosis of progress, risk assessment. 1997.
 50. Ron E. Thyroid cancer incidence among people living in areas contaminated by radiation from the Chernobyl accident. *Health Phys.* 2007; 93(5):502–511. [PubMed: 18049226]
 51. Gembicki M, Stozharov AN, Arinchin AN, Moschik KV, Petrenko S, Khmara IM, et al. Iodine deficiency in Belarusian children as a possible factor stimulating the irradiation of the thyroid

- gland during the Chernobyl catastrophe. *Environ Health Perspect.* 1997; 105 (Suppl 6):1487–1490. [PubMed: 9467069]
52. Robbins J, Dunn JT, Bouville A, Kravchenko VI, Lubin J, Petrenko S, et al. Iodine nutrition and the risk from radioactive iodine: a workshop report in the chernobyl long-term follow-up study. *Thyroid.* 2001; 11(5):487–491. [PubMed: 11396707]
 53. Liu XH, Chen GG, Vlantis AC, vanHasselt CA. Iodine mediated mechanisms and ththyroid carcinoma. *Crit Rev Clin Lab Sci.* 2009; 46(5–6):302–318. [PubMed: 19958216]
 54. Folley JH, Borges W, Yamawaki T. Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan. *Am J Med.* 1952; 13(3):311–321. [PubMed: 12985588]
 55. Parkin DM, Cardis E, Masuyer E, Friedl HP, Hansluwka H, Bobev D, et al. Childhood leukaemia following the Chernobyl accident: the European Childhood Leukaemia-Lymphoma Incidence Study (ECLIS). *Eur J Cancer.* 1993; 29A:87–95. [PubMed: 1445751]
 56. Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. *Br J Cancer.* 1996; 73(8):1006–1012. [PubMed: 8611419]
 57. Ivanov EP, Tolochko G, Lazarev VS, Shuvaeva L. Child leukaemia after Chernobyl. *Nature.* 1993; 365(6448):702. [PubMed: 8413648]
 58. Gapanovich VN, Iaroshevich RF, Shuvaeva LP, Becker SI, Nekolla EA, Kellerer AM. Childhood leukemia in Belarus before and after the Chernobyl accident: continued follow-up. *Radiat Environ Biophys.* 2001; 40(4):259–267. [PubMed: 11820734]
 59. Ivanov VK, Gorski AI, Tsyb AF, Khait SE. Post-Chernobyl leukemia and thyroid cancer incidence in children and adolescents in Bryansk region: an evaluation of risks. *Voprosy onkologii.* 2003; 49(4):445–449. [PubMed: 14569934]
 60. Ivanov, VK.; Tsyb, AF. Medical Radiological Effects of the Chernobyl Catastrophe on the Population of Russia: Estimation of Radiation Risks. Moscow, Meditsina: 2002.
 61. Noshchenko AG, Zamostyan PV, Bondar OY, Drozdova VD. Radiation-induced leukemia risk among those aged 0–20 at the time of the Chernobyl accident: a case-control study in the Ukraine. *Int J Cancer.* 2002; 99(4):609–618. [PubMed: 11992554]
 62. Davis S, Day RW, Kopecky KJ, Mahoney MC, McCarthy PL, Michalek AM, et al. Childhood leukaemia in Belarus, Russia, and Ukraine following the Chernobyl power station accident: results from an international collaborative population-based case-control study. *Int J Epidemiol.* 2005
 63. Noshchenko AG, Bondar OY, Drozdova VD. Radiation-induced leukemia among children age 0– years at the time of the Chernobyl accident. *Int J Cancer.* 17 8.2009
 64. Petridou E, Trichopoulos D, Dessypris N, Flytzani V, Haidas S, Kalmanti M, et al. Infant leukaemia after in utero exposure to radiation from Chernobyl [see comments]. *Nature.* 1996; 382:352–353. [PubMed: 8684463]
 65. Cardis E, Howe G, Ron E, Bebeshko V, Bogdanova T, Bouville A, et al. Cancer consequences of the Chernobyl accident: 20 years after. *J Radiol Prot.* 2006; 26(2):127–140. [PubMed: 16738412]
 66. Kesminiene A, Evrard AS, Ivanov VK, Malakhova IV, Kurtinaitis J, Stengrevics A, et al. Risk of hematological malignancies among Chernobyl liquidators. *Radiat Res.* 2008; 170(6):721–735. [PubMed: 19138033]
 67. Romanenko AE, Finch SC, Hatch M, Lubin JH, Bebeshko VG, Bazyka DA, et al. The Ukrainian-American study of leukemia and related disorders among Chornobyl cleanup workers from Ukraine: III. Radiation risks. *Radiat Res.* 2008; 170(6):711–720. [PubMed: 19138038]
 68. Kryuchkov V, Chumak V, Maceika E, Anspaugh LR, Cardis E, Bakhanova EV, et al. RADRUE method for reconstruction of external gamma doses to Chernobyl liquidators in epidemiological studies. *Health Phys.* 2009; 97(4):275–298. [PubMed: 19741357]
 69. Pukkala E, Kesminiene A, Poliakov S, Ryzhov A, Drozdovitch V, Kovgan L, et al. Breast cancer in Belarus and Ukraine after the Chernobyl accident. *Int J Cancer.* 2006; 119(3):651–658. [PubMed: 16506213]
 70. Bogdanova N, Antomenkova N, Rogov Y, Karstens J, Hilemans P, Dörk T. High frequency and allele-specific differences of BRCA1 founder mutations in breast cancer and ovarian cancer patients from Belarus. *Clin Genet.* 2010; 78(4):364–372. [PubMed: 20569256]

71. Cardis E, Hall J, Tavtigian SV. Identification of women with an increased risk of developing radiation-induced breast cancer. *Breast Cancer Res.* 2007; 9(3):106. [PubMed: 17617928]
72. Darby S, McGale P, Peto R, Granath F, Hall P, Ekbom A. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: nationwide cohort study of 90 000 Swedish women. *Br Med J.* 2003; 326(7383):256–257. [PubMed: 12560277]
73. Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. *JAMA.* 1993; 270(16):1949–1955. [PubMed: 8411552]
74. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. *Radiat Res.* 2003; 160(4):381–407. [PubMed: 12968934]
75. Little MP, Tawn EJ, Tzoulaki I, Wakeford R, Hildebrandt G, Paris F, et al. Review and meta-analysis of epidemiological associations between low/moderate doses of ionizing radiation and circulatory disease risks, and their possible mechanisms. *Radiat Environ Biophys.* 2010; 49(2): 139–153. [PubMed: 19862545]
76. Buzunov V. Epidemiology of non-cancer effects of ionizing radiation. *Bull Ukr Acad Med Sci.* 2006; 12(1):174–184.
77. Ivanov VK, Maksimov MA, Chekin SYu, Petrov AV, Biryukov AP, Kruglova ZG, et al. The risk of radiation-induced cerebrovascular disease in Chernobyl emergency workers. *Health Phys.* 2006; 90(3):199–207. [PubMed: 16505616]
78. ICRP. ICRP Publication 56. Oxford: International Commission for Radiological Protection. Pergamon Press; 1990. Age-dependent doses to members of the public from intakes of radionuclides: Part 1 - Ingestion dose coefficients.
79. ICRP. Publication 60, Annals of the ICRP. Vol. 21. Elsevier; Amsterdam: 1991. ICRP, 1990 Recommendations of the International Commission on Radiological Protection.
80. Worgul BV, Kundiyeu YI, Sergiyenko NM, Chumak VV, Vitte PM, Medvedovsky C, et al. Cataracts among Chernobyl clean-up workers: implications regarding permissible eye exposures. *Radiat Res.* 2007; 167(2):233–243. [PubMed: 17390731]
81. ICRP. Recommendations of the international commission on radiological protection. Vol. 60. Oxford: International Commission on Radiological Protection. Pergamon Press; 1991.
82. Drozdovitch V, Maceika E, Khrouch V, Zvonova I, Vlasov A, Bouville A, et al. Uncertainties in individual doses in a case control study of thyroid cancer after the Chernobyl accident. *Radiat Prot Dosimetry.* 2007 [Epub ahead of print].
83. Kopecky KJ, Stepanenko V, Rivkind N, Voilleque P, Onstad L, Shakhtarin V, et al. Childhood thyroid cancer, radiation dose from Chernobyl, and dose uncertainties in Bryansk Oblast, Russia: a population-based case-control study. *Radiat Res.* 2006; 166(2):367–374. [PubMed: 16881738]
84. Kesminiene A, Evrard AS, Ivanov VC, Malakhova IV, Kurtinaitis J, Stengrevics A, et al. Risk of Hematological Malignancies among Chernobyl Liquidators. *Radiation Research.* 2008; 170:721–735. [PubMed: 19138033]
85. Romanenko, AYe; Finch, SC.; Hatch, M.; Lubin, JH.; Bebeshko, VG.; Bazyka, DA., et al. The Ukrainian-American Study of Leukemia and Related Disorders among Chornobyl Cleanup Workers from Ukraine: III. Radiation Risks *Radiat Res.* 2008; 170:711–720.
86. Zablotska LB, Bogdanova TI, Ron E, Epstein OV, Robbins J, Likhtarev IA, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: dose-response analysis of thyroid follicular adenomas detected during first screening in Ukraine (1998–2000). *Am J Epidemiol.* 2008; 167(3):305–312. [PubMed: 17989057]