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REVIEW

Somatic health effects of Chernobyl: 30 years on

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Abstract 2016 marked the 30th anniversary of the Chernobyl Nuclear Power Plant accident. We and others wrote reviews for the 25th anniversary. Since then, additional papers have appeared and it seems timely to highlight lessons learned. To present, not a systematic review, but a commentary drawing attention to notable findings. We include not only recent reports and updates on previous results, but key findings from prior Chernobyl studies. The dose-dependent increase in Papillary Thyroid Cancer (PTC) following childhood I-131 exposure in Ukraine and Belarus has now been shown to persist for decades. Studies of post-Chernobyl PTCs have produced novel information on chromosomal rearrangements and gene fusions, critical to understanding molecular mechanisms. Studies of clean-up workers/liquidators suggest dose-related increases of thyroid cancer and hematological malignancies in adults. They also report increases in cardiovascular and cerebrovascular disease. If confirmed, these would have significant public health and radiation protection implications. The lens opacities following low to moderate doses found earlier are also a concern, particularly among interventional radiologists who may receive substantial lens doses. Finally, there is some, inconsistent, evidence for genetic effects among offspring of exposed persons. Further efforts, including improved dosimetry, collection of information on other risk factors, and continued follow-up/monitoring of established cohorts, could contribute importantly to further understand effects of low doses and dose-rates of radiation, particularly in young people, and ensure that appropriate public health and radiation protection systems are in place. This will require multinational collaborations and long-term funding.

Keywords Chernobyl · Thyroid cancer · Thyroid disease · Radiation · Leukemia · Cataracts · Cardiovascular diseases · Multinational collaborations

Introduction

Over 30 years now have passed since the Chernobyl Nuclear Power Plant explosion in northern Ukraine (and more than 5 years since a tsunami caused a major accident at the Fukushima Daiichi Power Plant in Japan). Although the effects of nuclear accidents on mental health and psychological well-being are a focus of concern [1], research results from Chernobyl clearly show significant impacts of radioactive fallout on a range of somatic health endpoints.

At the 25-year mark, we published a detailed review of the international peer-reviewed literature on somatic health effects post-Chernobyl [2], describing notable dose-related increases in papillary thyroid cancer (PTC) among children and adolescents exposed to radioiodines, and, among cleanup workers exposed primarily to external radiation, an elevated risk of cataracts, leukemia and, possibly, cardiovascular disease (CVD). At the time of the earlier review, we pointed to questions that remained—whether the thyroid cancer risk in exposed children would persist and what

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future tumors would look like, and whether exposure in utero or in later life also increased risk, all questions of importance to improve our radiation protection system. We cited several unresolved issues that might be addressed post-Chernobyl in further studies of exposed populations, including risk of breast cancer and childhood leukemia following radioiodine fallout.

In the years between the 25th and 30th anniversaries, a number of papers have appeared. Rather than a comprehensive review, we present here a brief Commentary on what we consider to be the highlights, including updates on the association between radiation from Chernobyl and thyroid disease in exposed children and adolescents, describing the pattern of risk over time and noting intriguing results from studies of the histopathology and molecular genetics of the post-Chernobyl PTCs. We comment also on new research (based on a PubMed search, 30th anniversary conference proceedings and contact with the principal investigators of the main Chernobyl studies). This includes in particular studies on cleanup workers from Ukraine, Russia and the Baltic countries exposed as adults, with limited but suggestive evidence of a dose-related risk not only for all types of leukemia as shown previously, but for both thyroid and non-thyroid solid cancer as well, possibly, as multiple myeloma. There are, in addition, recent reports on cardio- and cerebrovascular diseases among Russian and Ukrainian liquidators that need to be considered in the context of findings from other populations. In what follows we provide a summary and interpretation of the evidence, and point out where data are insufficient—including for earlier findings that have not been pursued—or where data continue to be lacking.

Discussion

Thyroid disease post-Chernobyl

Thyroid cancer

As we reported at the 25-year mark [2], the earliest and most striking health effect following the Chernobyl accident was unquestionably the increased risk of thyroid cancer among those exposed at an early age to Iodine-131 in fallout in Ukraine and Belarus, the countries most affected by radioactive releases from the damaged reactor. Increased risk was shown in numerous epidemiological studies, including the parallel cohort studies of ~26,000 exposed children and adolescents in Ukraine (UkrAm) and Belarus (BelAm) screened biennially for thyroid disease [3, 4]. On average children had higher doses due to their small thyroid mass and greater consumption of ^{131}I-contaminated milk. The mean doses, based on direct measurements and an ecologic model of environmental transfer, were 650 mGy in the UkrAm cohort and 680 mGy in BelAm. The respective dose-related risks for thyroid cancer were 5.25/Gy in UkrAm [3] and 2.15/Gy in BelAm [4]. Increased risks were also shown in case–control studies [5–7] and ecological studies [8]. The increase in thyroid cancer was greatest for those who were youngest at exposure (0–4 years), a trend that appears to extend to those exposed in utero [9]. Brenner et al. [10] have shown that the elevated risk of thyroid cancer in the UkrAm cohort has persisted for more than 2 decades post-exposure, with no significant decrease over time. Effects of dose-measurement error on the estimated risk—always a matter of concern—were addressed by Little et al. [11], who found that statistical correction for dosimetric errors has little impact (a reduction of about 8%) on radiation risk estimates. The magnitude of the estimated dose-dependent thyroid cancer risk following Chernobyl, the trends with age at exposure, and the persistent elevation over time are all similar to what has been seen with exposure to external radiation among Japanese atomic bomb survivors [12].

Although clearly not a factor in iodine-sufficient Japan, the iodine deficiency (ID) so common in Chernobyl-contaminated regions has been suggested to modify the effects of radiation since ID increases the absorbed dose to the thyroid (iodine deficient glands take up more radioiodine) and stimulates cellular proliferation, leading to a possible tumor promoting effect. The empirical data, however, are not entirely consistent on this point. An ecological study in Russia [13] and a case–control study in Belarus and Russia [6] comparing risks in subjects stratified by tertiles of soil iodine levels, as well as use of iodine prophylaxis in the latter, both showed a modifying effect of ID. Radiation-related risks were also increased in the BelAm cohort among subjects with indicators of iodine deficiency such as diffuse goiter or enlarged thyroid volume [4], consistent with the earlier studies. In the UkrAm study, neither iodine prophylaxis nor iodine deficiency as indicated by goiter and elevated levels of serum Tg had statistically significant modifying effects on I-131-related risk, although trends were in the expected direction [10]. Iodine deficiency thus deserves careful attention in future studies of radiation-related thyroid cancer. A single ecologic study has recently suggested that, in Belarus, exposure to nitrates in drinking water might also have a modifying effect on radiation risk of thyroid cancers, by, for example, contributing to thyroid hyperplasia [14].

An important question following the Chernobyl accident is whether exposure to ^{131}I may also confer an increased risk of thyroid cancer in adults. Increases in incidence have been reported among Russian [15] and Baltic clean-up workers [16], particularly among those who worked in the first months after the accident when ^{131}I exposure could

occur. A case–control study, nested within the cohorts of Belarus, Russian and Baltic cleanup workers [17]—with individual dose reconstruction,—also found a dose-dependent increase in thyroid cancer risk. The risk estimate was similar for microcarcinomas and for larger tumors, as well as for tumors with and without lymph node involvement, suggesting thyroid screening is unlikely to entirely account for the observation. Recall bias and dosimetric uncertainties could, however, play a role. A recent report of the Atomic Bomb Life Span Study (LSS) [12] found a persistent elevation in risk more than 50 years post-exposure, but only among those exposed before age 20. Clearly, further research is needed to determine the association between radiation exposure at later ages and thyroid cancer risk.

In recent years, there have been a number of studies on the distinctive histopathology of the post-Chernobyl PTCs among exposed children and adolescents. It was reported early on that the pediatric thyroid cancers post-Chernobyl were PTCs of the solid/follicular subtype with a high prevalence of RET/PTC rearrangements, in particular PTC3, which seem to correlate with the solid growth pattern [18]. Non-encapsulated PTCs were common and there was typically evidence of tumor invasiveness. Associations between histopathologic features and I-131 dose have been further analyzed in both the UkrAm [19] and BelAm [20] cohorts. In BelAm, dose was associated with solid/diffusing variants and indicators of tumor aggressiveness. In UkrAm, aggressive properties of PTCs appeared to be associated with dose and with chromosomal translocations.

There has also been considerable molecular biology work in post-Chernobyl pediatric thyroid cancers. As thyroid cancers in young people are generally very rare, these are considered a unique resource for investigating radiation-carcinogenesis. Recent studies using DNA and RNA aliquots extracted from UkrAm samples stored at the Chernobyl Tissue Bank [21, 22] have linked I-131 dose to recurrent somatic alterations and altered expression of certain genes. In an assessment of mRNA expression patterns, 11 genes with differential dose expression (in paired samples of tumor and normal tissue) were identified and validated, and altered dose-dependent gene expression was found in an additional 8 genes in tumor tissue [23] and 6 genes in normal tissue [24]. Dose–response relationships have also been evaluated for somatic alterations such as RET/PTC that frequently occur in radiation-related thyroid cancers [25]. Leeman-Neill et al. [26] have reported a link between I-131 dose and RET/PTC, a gene fusion seen in 30–80% of post-Chernobyl cancers, as well as PAX8/PPARE rearrangements and, as expected, an inverse association with BRAF and RAS point mutations which are common in sporadic PTCs. The same group has identified ETV6-NTRK3 as a common rearrangement in the UkrAm tumors [27]. Ito et al. [28] have reported that similar rearrangements of RET can be induced by in vitro irradiation of thyroid tumor cells. Gene fusions (such as between ETV6 and NTRK3), infrequently seen in sporadic PTCs, have been found in several tumor types, raising the possibility that fusions may be an important mechanism of radiation carcinogenesis [29].

A DNA copy number gain on chromosomal band 7q11.23 and mRNA overexpression of CLIP2 have also been found in post-Chernobyl PTCs [30, 31] and CLIP 2 has been proposed as a biomarker of radiation-related PTC. This was recently tested in a model estimating radiation risk from marker measurements, with results suggesting a path of PTC development with CLIP2 as the driver gene [32]. The search for a radiation signature needs to continue.

Benign thyroid disease

Unlike thyroid cancer, the effects of relatively low dose ^{131}I on benign thyroid diseases have rarely been studied. They have been, however, the focus of recent research in the UkrAm and BelAm screening cohorts of exposed children and adolescents, where associations between structural (follicular adenoma) and functional (hypothyroidism, hyperthyroidism) endpoints and ^{131}I dose have been investigated. A 2006 study on the UkrAm cohort showed no association between ^{131}I and autoimmune thyroiditis but did find elevations in ATPO (antibodies to thyroid peroxidase) [33]. Since then, a linear dose–response relationship with follicular adenoma (FA), a benign neoplastic thyroid nodule, has been reported in UkrAm [34], and the association confirmed in the BelAm cohort [35], with similar two-fold excess risks seen in both. Risks were highest in those youngest at exposure; in neither cohort were there clear indications of effect modification by iodine deficiency. A recent study in the BelAm cohort [36] has also found a dose-dependent risk of screening-detected non-neoplastic thyroid nodules $\geq$10 mm, as well as of neoplastic nodules (in particular follicular adenoma), with the effect strongest among those younger at exposure.

In terms of functional thyroid diseases, a small association was found between ^{131}I dose and prevalent subclinical hypothyroidism (EOR/Gy = 0.10, 95% CI 0.03–0.21) in the UkrAm cohort [37] and confirmed in the BelAm cohort (EOR/Gy = 0.34, 95% CI 0.15, 0.62) [38]. No association was found with prevalent hyperthyroidism [39] or other measures of thyroid function. As with FA, there was effect modification of hypothyroidism by age at exposure but not with indicators of ID.

In summary, it appears that ^{131}I increased not only the risk of thyroid cancer in those exposed to Chernobyl fallout at young ages, but also the risks of follicular adenoma and

hypothyroidism—both quite common benign thyroid diseases.

Other endpoints

General population

As indicated in our 25th anniversary review, doses to organs other than the thyroid tended to be low in the general population and hence studies of effects other than thyroid cancer have limited statistical power. An ecological study published in 2006 [40] suggested a possible dose-related increase in the risk of breast cancer among young women in the most contaminated districts of Belarus and Ukraine, but, unfortunately, this finding has not yet been followed up in analytic studies. The issue of breast cancer following low-dose radiation is an important one, as we suggested in our 25th Anniversary Review, and should be pursued.

Leukemia after low-dose radiation is also of interest, since, like thyroid and breast, this is a highly radiosensitive neoplasm. There were some earlier studies of those exposed as children or in utero but, as we noted in our previous review, these generally had limited statistical power and the results were inconsistent. More recent standardized incidence ratios (SIR) analyses of non-thyroid cancers in the UkrAm [41] and BelAm [42] cohorts, based on linkage with the national cancer registries, did find similar elevations in leukemia (in UkrAm, SIR = 1.92, 95% CI 0.69, 4.13; in BelAm, SIR = 1.78, 95% CI 0.71, 3.61), but cases were few (n = 5 and 6, respectively) and there was only limited statistical power to detect effects.

Concerning adults, recent publications from Ukraine suggest increased risk of breast cancer [43, 44], endocrine diseases [45] and cardiovascular mortality [46] among residents of contaminated areas. However, these studies lack adequate dosimetry, completeness of follow-up is uncertain and no information is available about other risk factors for these diseases.

Because of concern about potential long-term genetic effects of parental irradiation, studies have been carried out on the frequency of minisatellite mutations in children born after Chernobyl in contaminated areas of Ukraine and Belarus [47, 48]. Elevations have been suggested. However, these results contrast with negative findings in offspring of Chernobyl clean-up workers [49] as well as of A-bomb survivors [50]. The minisatellite data from Ukraine suggest a far lower doubling dose than expected from animal work, and there have been some concerns regarding the adequacy of the dosimetry and potential confounding by other exposures [51]. Although no firm conclusion can yet be drawn, the extent of heritable and de novo mutation rates following radiation exposure remains an important issue and is currently being pursued in an NCI-supported "Trio" Study in Ukraine, in which at least one parent was exposed to Chernobyl radiation as a clean-up worker and/or evacuee from a contaminated area. Using whole genome sequencing, the Trio Study searches for mutational patterns in the exposed parent(s) that may have been transmitted to a child born more than 1 year after the Chernobyl accident.

Cognitive effects have been studied in children exposed to radiation from Chernobyl while in utero or as infants but the evidence has been inconsistent (reviewed in [52]).

Clean-up workers

In addition to the possible increased risk of thyroid cancer (discussed above), we reported earlier [2] that increases in risk of leukemia from external radiation exposure have been seen in nested case–control studies of clean-up workers in the Baltic countries, Belarus, Russia and Ukraine [53, 54]. These studies relied on detailed individual red bone-marrow dose reconstruction, based on site dose rate measurements and modelling and on information collected by questionnaire on the worker's activities, type, place, time and conditions of work in the 30 km exclusion zone [55]. A more recent case–control study among Ukrainian liquidators [56] has since replicated the increased risk of leukemia, as well as the earlier observation of a similar risk for chronic lymphocytic leukemia (CLL), previously considered non-radiogenic, and non-CLL leukemia. Cohort follow-up of clean-up workers included in the State Chernobyl Registries in Russia [57] also show increased risks for non-CLL leukemia (CLL was not assessed), and suggest that the risk may decrease with time since the accident.

In Ukraine, increased incidences of multiple myeloma (MM) and of myelodysplastic syndrome were also reported, in comparison with the general population, though analysis by dose level or time or duration of work as a clean-up worker was not presented [58]. While increases in MM have been seen in other studies, in particular in mortality studies of the atomic bomb survivors and in some studies of nuclear industry workers [59–61], a significant dose–response has not been seen in recent incidence studies of atomic bomb survivors [62] and hence the relation between radiation exposure and MM is at present unclear.

Finally, Kashcheev et al. [63] reported a dose-related increase in the incidence of solid cancers among Russian clean-up workers included in the State Chernobyl Registry. While the completeness of case ascertainment is uncertain for this cohort, this result is complemented by a similar increase in solid cancer mortality, an outcome not subject to a possible surveillance bias. The ERR/Gy was 0.47 (95%

CI 0.03, 0.96), similar to that obtained in recent pooled studies of nuclear industry workers [64] and compatible with extrapolations from studies of atomic bomb survivors.

An important earlier finding is the increased risk of cataracts, in particular posterior sub-capsular lens opacities, in a screened cohort of Ukrainian clean-up workers [65] which has led the International Commission for Radiological Protection to revise its recommendations downward for maximum dose to the lens of the eye [66]. However, no follow-up of this important cohort has been conducted in recent years.

In the 25th anniversary review we mentioned the finding of a dose-related increased risk of cerebrovascular and ischemic heart disease among Russian clean-up workers [67], though no information was available to adjust for other risk factors. The follow-up of this cohort, based on the State Chernobyl Registry, was extended by 12 years, up to 2012, confirming the increase in cerebrovascular disease [68]—excess relative risk (ERR/Gy = 0.45, 95% CI 0.28, 0.62); again, no information was available on other risk factors but the authors adjusted risk estimates for concomitant diseases such as diabetes. A study of Ukrainian clean-up workers of the 1986–1987 period, based on data from the National Research Center for Radiation Medicine's Clinico-Epidemiological Registry, found a dose-related increased risk of both cardiovascular disease and cerebrovascular disease [69, 70]. However, there may be questions about the completeness and accuracy of disease registration as well as the adequacy of the dose estimates, and although a number of non-radiation risks were identified, except for age, confounding factors were not taken into account. These results, therefore, need further confirmation.

There has been interest in the possibility of telomere shortening—a biomarker for biological aging—in workers exposed to protracted low-dose radiation. This was suggested in a small study of Chernobyl workers from Ukraine [71]. However, a study of about 600 clean-up workers in Latvia whose leukocytes were analysed 2 decades after exposure, along with a sex- and age-matched control group, found the reverse: longer telomeres among those exposed in 1986 and involved in 'dirty' tasks [72]; this was interpreted as reflecting defects in telomerase regulation.

Neuropsychological changes and cognitive deficits have also been studied among Chernobyl clean-up workers but are outside the scope of this review.

Conclusions and perspectives

While psycho-social effects are without doubt the most important public health consequence of the accident—and can be found, on a similar scale, following the Fukushima accident which resulted in generally much lower doses—careful studies of the most exposed populations have provided important information about radiation risks following exposure to ^{131}I, as well as on the effects of protracted low dose, low dose-rate exposures to a mixture of external and internal (mainly ^{137}Cs) radiation. These are of great relevance to radiation protection.

Thirty years after Chernobyl, nearly 11,000 thyroid cancers cases have been reported among those who were children or adolescents at the time of the accident in Belarus, Ukraine and the most contaminated regions of Russia [73]. The spontaneous incidence of thyroid cancer increases rapidly in adolescence and adulthood, and not all of these cases can be attributed to radiation from the accident (in first 25 years, it was estimated that about half of these were radiation-induced, with the proportion being higher in Belarus, particularly in the most contaminated region of Gomel) but there has unquestionably been a substantial dose-dependent excess risk of I-131-related post-Chernobyl thyroid cancers—many with a distinctive histopathology—that has now persisted for decades. Studies of PTCs in the affected territories, using the Chernobyl Tissue Bank as a resource, have included in-depth molecular biological work based on the UkrAm cohort of exposed children. This has produced novel information on molecular profiles of the tumors—including chromosomal rearrangements and gene fusions—of great importance for understanding the pathogenesis of thyroid cancer in the presence of ionizing radiation. Studies of thyroid cancer following exposure in utero have suggested risks of the same order, or larger, than that following similar exposures in infancy. Investigation of established cohorts of clean-up workers has produced new data on thyroid cancer risk in exposed adults, suggesting that it may exist and may not be much smaller than the risk observed in exposed children. In addition, the recent work extends the evidence on risk of hematological malignancies among Chernobyl workers (including, possibly, CLL and MM), and, perhaps most importantly for public health and radiation protection, on possible risk of CVD. There are also some intriguing findings related to telomere length changes in clean-up workers. Lens opacities following low to moderate doses are a growing concern, particularly among medical professionals involved in interventional radiology and cardiology. Finally, there is some, though not consistent, evidence for possible genetic effects of exposures among offspring of exposed persons.

Although much critical knowledge about radiation effects and factors which may modify them has been drawn from the Chernobyl experience, there is yet more that can be learned, including the pattern of risk in the long term and the effects of exposure in adulthood as well as prenatally and in infancy. Continued efforts, including

improvements in dosimetry and follow-up of clean-up workers with collection of information on lifestyle and other risk factors for chronic diseases in this population, and monitoring of the established cohorts of those exposed in utero and in early life, would improve our understanding of low dose radiation risks—and possibly mechanisms of radiation carcinogenesis—and ensure that our system of radiation protection is fully adequate.

Such endeavors, however, require multinational collaborations and funding, first to ensure maintenance of important infrastructures—high quality cancer registries and health care information systems, as well as archives such as the Chernobyl Tissue Bank. It will also be important to encourage sharing and even pooling of data on exposure conditions and disease outcomes in populations from all the affected countries. Combined/pooled analyses will require sophisticated techniques to deal with issues such as heterogeneity, dosimetric errors, confounding and the effects of multiple testing. Financial support will be needed for infrastructure.

NIH has made a substantial, continuing commitment to Chernobyl research over the last 25 years and so, until recently, have the EU and Japan. The governments and scientists of the most affected states, of course, have made and continue to make enormous efforts in the follow-up to the accident. Only through continued collaborative, multinational efforts, however, will we be able to draw the full lessons of the accident for radiological protection in general and for assessing the consequences of Fukushima and any possible future nuclear accidents.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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