PROJECT PROPOSALS FOR URGENT PRIORITIES

The accident at the Chernobyl Nuclear Power Plant in 1986 took place in a European country, the radiation from the accident badly affected three European countries, and fallout from the accident reached every European country. Many hundreds of people were affected by direct whole body radiation through their work on the plant during and after the accident. Millions of people were exposed to significant levels of radiation from fallout, making this accident unique. The health consequences of radiation exposure may be long delayed, as shown from the study of atomic bomb survivors in Japan. The type and tissue distribution of the radiation from the bombs differs from that from fallout making the long term consequences of Chernobyl unpredictable. Without proper study of the consequences information of great potential scientific value and of great importance to radiation protection will be lost. In addition speculation will be unconstrained, and will influence public attitudes to the perceived dangers of radiation. With this background the EC sought advice on the requirements for future work on the health consequences of the accident.

The ARCH programme was supported by the EC in 2008. The main deliverable was the production of a strategic research agenda (SRA) for studies of the health consequences of the Chernobyl accident. This would be carried out through the interaction of a core group with an international group of experts and advisors. During the development of the SRA some topics would be identified as of urgent high priority; these would be reported to the EC as the Work Package 1 deliverable.

The Core Group has met on 4 occasions; it has identified 26 possible areas for research. Draft papers outlining the background, aims, details of a possible approach and methods that could be applied, together with potential roadblocks were prepared for each topic. The topics and the papers have been discussed at two meetings of the Expert group and Advisors, modifications were suggested and two additional subjects proposed by the experts.

At the last meeting the priority to be given to each topic was assessed using agreed criteria (Annex A), and five research proposals of the 28 were considered to be of short term priority. In addition, the experts regarded it as urgent to carry out small scale exploratory work in order that the feasibility and scope of three other projects could be adequately assessed for the SRA. Finally one infrastructure project was regarded as very important, but this part of this proposal involved international cooperation, including the USA. No progress could be made without an initial approach to the US National Cancer Institute, followed by approaches to the authorities in Belarus and Ukraine to see whether current US funded programmes in those countries which are being scaled back could be extended as joint programmes with the EC.

The recommended projects are set out below.

Proposal 1

Monitoring of Cancer Trends

Background

The main health effect of radiation from the Chernobyl accident observed to date is a dramatic increase in the incidence of thyroid cancer in persons exposed as young people (1). Increases in the incidence of a number of other types of cancer, in particular breast cancer, have also been reported but have not yet been conclusively demonstrated to be related to radiation from the accident (2). Continued surveillance of trends in the incidence of cancers, including thyroid cancer, is an important priority to evaluate the public health impact of the accident and should continue until the complete burden of this disease caused by the accident has been fully characterized.

Objective

To monitor trends in overall and site-specific cancer incidence in the affected areas including Europe as a whole.

Justification

This is the first (and hopefully last) occasion on which population exposure to non-negligible levels of radiation has occurred on such a scale. The number of thyroid cancers diagnosed among those who were children and adolescents at the time of the accident is unprecedented and the future of the endemic is an important public health and health services concern in the most contaminated countries, which must be evaluated. Surveillance of incidence trends for other cancers is also an important priority both in terms of public health and health care delivery planning and radiation protection research.

Proposal

To conduct routine surveillance of cancer incidence and mortality trends using existing data from population based cancer registries.

Study approach

Trends in diseases are most efficiently studied using ecological designs, relying on existing data from population based cancer registries to continuously monitor trends in those exposed at different ages. Incidence studies are more informative than mortality studies in capturing the full burden of diseases, in particular for cancers such as thyroid cancer that typically have very good survival.

Dosimetry

Simple monitoring of tumour trends in populations does not require individual level doses.

Average doses to the thyroid (so-called "passport doses") have been calculated at the level of individual settlements in Belarus and contaminated regions of Russia and Ukraine and used in ecological studies to date (see for example (3)). In Europe outside of the most contaminated countries, average doses have also been estimated (4;5). Thus adequate dose estimation is possible and available for future ecological studies.

Feasibility

Ecological studies are routinely conducted to examine disease trend over time. Given the existence of population based cancer registries in Belarus and in the most contaminated regions of Ukraine and Russia, as well as in many other European countries it is quite feasible to conduct this type of study in the Chernobyl context to determine future trends. Such studies are generally quite economical and can be conducted periodically in the future as the necessary data are collected routinely.

Next steps

A project to monitor cancer trends should

- Arrange a meeting of staff responsible for maintaining Chernobyl registries to review comparability of information and feasibility of harmonising data collected and approaches
- Establish a trans-national steering committee to overview harmonisation, plan joint analyses and review proposals from other groups for use of data

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Proposal 2

Trends in infant and childhood leukaemia

Background

Studies of infant leukaemia conducted in several European countries did not provide unequivocal evidence about increased risk of leukaemia in those exposed *in utero* due to the Chernobyl accident. Although several have demonstrated a possible association, they did not show a clear trend with regard to radionuclide contamination levels. The major limitations of most of the studies are lack of individual dose estimates and very small number of cases included in the analyses.

Several ecological studies have also examined the association between leukaemia risk and exposure to radiation from the Chernobyl accident in childhood, including the European Childhood Leukaemia-Lymphoma Study (ECLIS), the largest and most comprehensive study to date (1;2). The ECLIS study found no evidence of a radiation-related increase in incidence of leukaemia in Europe in the first five years after the accident. The ECLIS study encountered problems to assess specifically the issue of exposure *in utero* because a number of cancer registries, particularly in Eastern European countries, collect year rather than exact date of birth.

Objective

- To investigate if there is an increase in leukaemia among those who were exposed early in life, in particular *in utero*

Justification

Studies of leukaemia among individuals exposed *in utero* or in infancy as a result of the Chernobyl accident are very important for radiation protection purposes as they may provide evidence on the increased susceptibility in these particularly sensitive populations. Studies of childhood leukaemia incidence trends following the Chernobyl accident are of scientific and public health importance due to unique nature of population and exposure conditions, namely, low-dose rate protracted environmental exposure.

Study approach

Proposed approach is the evaluation of leukaemia incidence and mortality trends among those who could have been exposed *in utero* and/or in childhood through existing cancer registries. A study of infant leukaemia assessing possible effect of exposure *in utero* should collect additional data (including the exact date of birth) from the European childhood cancer registries that participated in ECLIS study.

Dosimetry

Ecological approaches do not require individual level doses. Average doses to the foetus (whole body and/ or red bone marrow) and to the child's bone marrow should be in principle feasible in the contaminated regions of Belarus, Russia and Ukraine, as well as in Europe outside of the most contaminated countries and used in ecological studies to date (3).

Feasibility

There is considerable interest in seeing the ECLIS analyses redone and completed, but this would require a sizeable effort to collect the needed information from hospitals and population registries, if ethics approvals can be obtained.

Next steps

A project to study infant and childhood leukaemia should

- Contact Childhood Cancer Registries in Europe that participated in ECLIS study to review availability of exact dates of birth and feasibility to collect this information from hospital records and population registries
- Set-up a dosimetry committee to evaluate average doses to the foetus (whole body and/ or red bone marrow) and to the child's bone marrow in the participating countries
- Establish a steering committee to coordinate data collection and analyses

Reference List

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Proposal 3

Molecular Evolution and Molecular Epidemiology of Thyroid Tumours

Background

The greatly increased incidence of thyroid carcinomas in those exposed to fallout from the Chernobyl accident in the 3 most affected countries is well established. The WHO/IAEA 20 year conference estimated the numbers as 4,000 (1) and these have been described as the largest numbers of tumours of one type due to one cause on one date that have ever occurred (2). A dose effect relationship has been demonstrated (3). The situation however is more complex than the simple statement that radiation to the thyroid causes thyroid cancer. It was shown in the first few years after the increase was noticed that the risk of developing thyroid cancer was strongly correlated with age at exposure, with the youngest exposed having the highest risk (4). The morphological type of thyroid cancer was virtually always papillary carcinoma, and the commonest molecular change identified was rearrangement of the *RET* oncogene. With increasing latency there have been changes in the morphology, in the molecular pathology and in the clinical behaviour of the tumours. In the first 20 years papillary carcinomas remain by far the most dominant type, the small drop in proportion that they form of all thyroid carcinoma could reflect a fall in the attributable fraction. However both the subtype of papillary carcinoma and the type of *RET* rearrangement have changed with increasing latency, with the solid type of papillary carcinoma linked to *RET-PTC-3* becoming less frequent, and the classic type of papillary carcinoma linked to *RET-PTC-1* becoming more frequent (2;5;6). The clinical behaviour of the papillary carcinomas has also become less aggressive with increasing latency (7). These changes make forecasting the future course of the epidemic difficult; it is likely that the subtypes of papillary carcinoma and the molecular findings will continue to change, and it is also possible that follicular tumours, both benign and malignant, or other thyroid tumour types such as anaplastic carcinomas or medullary carcinomas may show a radiation related increase in incidence. It is therefore important that as well as following the overall incidence of thyroid carcinoma, the changes in the morphology, molecular pathology and clinical behaviour continue to be followed, to give a complete understanding of the consequences of exposure of a large population to fallout from a nuclear accident.

These studies however do not directly address two other important questions – are there specific changes in the tumour genome that are markers of radiation exposure, and are there germline changes which confer susceptibility to radiation induced thyroid cancers. Work so far has in general identified changes in the thyroid carcinomas found in populations exposed to Chernobyl fallout without adequate unexposed controls for the same ethnic background, so that for example it is difficult to know whether the relative lack of *BRAF* point mutation in the radiation related papillary carcinomas (8) is due to the tendency of radiation to induce double strand breaks, a necessary precursor to the development of oncogenes activated by rearrangement, or solely to the young age of the patients investigated. The presence in a minority of the thyroid cancer patients exposed to Chernobyl fallout of a family history of thyroid cancer (9) would suggest that germline changes conferring susceptibility to the development of thyroid cancer could be relevant. Germline mutations conferring susceptibility specifically to radiation induced thyroid carcinoma might not be associated with a family history of thyroid carcinoma, other than an increased risk for exposed siblings. Little is known of the genes associated with non-radiation induced familial papillary thyroid carcinoma

other than in certain specific types, current studies are investigating the role of germ line DNA polymorphisms in the susceptibility to thyroid cancer (10;11). A great deal is known about the genes involved in repair of radiation induced damage to DNA, see for example recent reviews (12;13). Polymorphisms in two genes involved in double strand break repair, *CHEK2* and *XRCC3*, have been associated with an increased risk for thyroid cancer. The suggestion that the increased incidence of thyroid cancers after radiation exposure is primarily due to the induction of double strand breaks which give rise to oncogenic mutations, and that the presence of germline changes reducing the efficiency of double strand break repair confers increased susceptibility to radiation induced thyroid cancer is an attractive and testable hypothesis.

Objective

To understand the mechanisms by which radiation-induced DNA damage gives rise to thyroid cancer by:
a) Studying the sequential molecular changes in Chernobyl related thyroid carcinomas with increasing latency, correlating these with changes in tumour type and morphology, and with clinical behaviour.
b) Analysing the molecular changes in thyroid tumours for radiation specific changes.
c) Studying germline DNA in patients with thyroid carcinomas to identify changes conferring increased susceptibility to thyroid carcinogenesis

Study approach

These objectives can be achieved in two separate but complementary approaches:

- Studies of a defined cohort with known thyroid doses. Identification of molecular findings in thyroid tumours, and correlation with morphology, dose, age at exposure, latency and clinical behaviour together with analysis of germline changes and correlation with dose related risk and with family history. The molecular techniques used could range from simple identification of oncogenes or DNA repair genes known to be relevant to whole genome analysis using the best available techniques. The BelAm and UkrAm cohorts *(see section on Life-span cohorts)* would be a useful study group if regular screening could be continued, as it would allow comparison of tumours from patients with a known high radiation dose and a correspondingly high attributable fraction with those from patients with a very low dose and a very high chance of being sporadic tumours; but still from the same ethnic group and sharing many environmental factors. Surveillance through tumour registries would not be adequate because follicular adenomas would not be included, and molecular and morphological studies would be extremely difficult. The distinction between a cellular follicular adenoma and a low grade follicular carcinoma is well known to be difficult, and a uniform standard of diagnosis requires review of all cases.
- An ecologic study of patients with thyroid tumours operated at the major centres in Minsk or Kiev would also be of value, as it would provide many more cases of known latency for the morphologic and molecular studies than could any study of existing cohorts. The success of such an approach, however, would depend on the availability of biological tissues on all of the cases and on appropriate documentation of referral patterns from study regions to ensure that cases are representative of the populations from which they arose and that no bias related to severity and prognosis is introduced by focusing on the cases referred to the participating centres. For greater efficiency, such a study should probably be restricted to those exposed at young ages in areas of high fallout levels.

Population

Children recruited to the BelAm and UkrAm cohorts would be a suitable population to address this study objective. In these cohorts, 11,918 children from Belarus and 13,243 children from the Ukraine were recruited into the study. This cohort was screened every 2 years for thyroid disorders. At each screening, each cohort member provided blood and spot urine samples, underwent thyroid palpation and ultrasound examination, and information was collected on medical history, and other information that could be useful in estimating thyroid dose.

Study Design

Given that relevant cohorts (e.g., BelAm and UkrAm cohorts) have already been assembled and necessary data has been collected, continued active follow-up of these cohorts would be needed to in addressing these objectives. The ecologic study could be based on a continued study of operative specimens of thyroid tumours from those exposed as children coming from areas with a known high level of fallout exposure together with study of germline changes.

Dosimetry

Individual thyroid doses from ^{131}I have been calculated based on direct thyroid measurements, for all subjects in these cohorts and doses from intake of long-lived nuclides and from external radiation are being calculated. Thus all needed dosimetric information would be available for the cohort study.

Biological samples

The most important material needed in this study would be blood and tumour tissue which should be available in further active follow-ups of these cohorts and from the ecologic study. Nucleic acid extracted from these samples and from samples from the ecological study should if possible be stored in a biobank for future study.

Data collection

Individual level information on potential modifiers of risk and on potential risk factors for thyroid tumours as well as the relevant clinical data including family history of thyroid or other tumours could be collected during the active screening if information is not already available.

Molecular changes

Two approaches could be used to follow the molecular evolution of the epidemic of thyroid cancer, analysis of known genes and genome wide association studies. Changes in the frequency of occurrence of genes known to be associated with thyroid carcinoma should be investigated. Currently these would include *RET, TRK, BRAF* and *PPAR* gamma rearrangements, and *BRAF* and *RAS* point mutations. Further genes could be added, either where newly discovered or where related to particular tumour types, including those linked to inherited thyroid cancer syndromes eg *P53, PTEN, APC, BCatenin, GRIM19*. More modern techniques studying the whole genome such as exome and whole-genome sequencing and genome wide association studies should also be used,

and preservation of nucleic acids for use in more powerful techniques being developed is extremely important.

The study of the molecular epidemiology would be based on the same patients as the study of the molecular evolution of the thyroid tumours, and could also be based on studies of known genes or on whole genome studies. Germline mutation in genes involved in DNA repair, particularly double strand break repair, could be studied, eg *BRACA1* and *2, RAD 50* and *51, ATM, NBJ1* and *XRCC4*. More modern techniques such as exome sequencing and genome wide association studies should also be used and genome wide association studies could be used to confirm and extend recent observations linking certain polymorphisms to thyroid carcinoma and particularly to radiation induced thyroid carcinoma The availability of a population with known doses would be a great advantage, because of the higher attributable fraction at high doses.

Feasibility

While data from study subjects are already collected, the main issue in addressing the feasibility of the cohort study is whether it will be possible to collaborate with the Belarus, Ukraine and US investigators and agencies that have set-up and followed up these cohorts already. Ethical issues apply to both approaches, and collaboration with a major centre such as Minsk will be needed for the ecologic study.

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Proposal 4
Breast cancer

Background

Breast cancer is the most common cancer and one of the leading causes of death from cancer in women worldwide. The female breast is considered to be one of the most radiosensitive organs/tissues (1;2).

There is mounting evidence that women carriers of pathogenic DNA repair and damage recognition genes may have an increased risk of breast cancer following exposure to ionizing radiation even at low doses (3). Worldwide increase in use of medical diagnostic and therapeutic radiation raises the question as to whether women are sufficiently well protected from developing iatrogenic breast cancer.

The descriptive epidemiological study conducted by Pukkala *et al* observed an increase in breast cancer risk, in particular among women who were below the age of 45 at the time of the accident and resided in the most contaminated districts of Belarus and Ukraine after the Chernobyl accident, and suggested that this increase may be radiation-related (4).

Objectives

To determine whether the reported increased rates of breast cancer in regions contaminated after the Chernobyl accident are related to dose to the breast.

If this is demonstrated, to study potential risk modifiers in this population, including possible genetic predisposition.

Justification

Women residing in the most contaminated districts near the Chernobyl NPP form an informative population to better quantify risks of breast cancer associated with low and protracted exposures and possibly identify factors that may contribute to increased individual sensitivity to these exposures because of their important numbers and because they received relatively high doses from the Chernobyl fall-out.

Eastern European populations carry important founder mutations in *CHEK2* , a gene involved in DNA damage recognition and repair. If an increased risk does exist after the Chernobyl accident, the population exposed is particularly well suited to study the possible role of individual susceptibility in radiation-induced breast cancer risk.

The results of this study have important public health implications in countries affected by the Chernobyl accident.

Proposal

A population-based case-control study would be the most cost-efficient approach to elucidate the aetiology of breast cancer in the most contaminated districts. Feasibility of setting up a case-control study of breast cancer risk was evaluated in 2003-2005 in Belarus and Ukraine (5). The study was proved to be feasible. Study documents, including questionnaire, protocol, and procedures document, were developed and tested. Collaborations with local hospitals were established. Pathology departments for obtaining fresh tumour tissue, laboratories for extracting DNA, performing

immunohistochemistry and logistics for transportation of biological material were identified and tested.

To conduct a case-control study of breast cancer in women who were exposed early in life to the Chernobyl fall-out.

Proposed Approach

Case-control studies (retrospective and prospective) could be conducted in the territories with potentially high exposure levels where relative numbers of radiation induced breast cancers are expected to be the highest compared to "background" rates. Potential areas are: the most contaminated districts of Gomel and Mogilev regions in Belarus; Chernigov, Kiev and Zhitomir region in Ukraine. Since the age at exposure is a very important modifier of risk, it is expected that the increase would be higher and easier to detect in women who were less than 35 at the time of the Chernobyl accident (26 April 1986). Case ascertainment and recruitment can be conducted through establishing contacts with all potential treatment and diagnostic hospitals within the study area. Completeness of case ascertainment can be verified through cancer registries. Individual information on risk factors can be collected through a study questionnaire (draft questionnaire for a potential case-control study was developed in a previous study coordinated by IARC (5), diagnostic information for cases can obtained through checking medical records in the participating hospitals.

Population based controls can be selected through existing regional population registries in Belarus and Ukraine.

In the framework of case-control studies biological samples including breast tumour tissues, blood and buccal smears or saliva, might be collected to identify mutations responsible for the genetic susceptibility of radiation induced cancers.

Dosimetry

An approach developed to reconstruct individual doses (and uncertainties) to the breast within the study coordinated by IARC could be applied in the case-control study (5). The approach considers following exposure pathways that may contribute to the dose to the breast:

- External exposure from gamma-emitting radionuclides deposited on the ground;
- Internal exposure from ingestion of long-lived isotopes such as ^{134}Cs and ^{137}Cs;
- Internal exposure from ^{131}I intake.

Biological samples

Samples (fresh breast tumour tissues and blood or saliva) could be collected following the assessment of study power.

Molecular markers

Blood and buccal smears or saliva samples will be needed for screening mutations identified to contribute to genetic susceptibility of radiation induced breast cancer.

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Proposal 5

Radiation induced cataracts in liquidators

Background

The lens of the eye is considered a radiosensitive tissue, posterior subcapsular and cortical opacities are associated with exposure to ionizing radiation (1;2).
The results of recent epidemiological studies showing an increased cataract risk after low-dose dose exposure provoked considerable debate about the deterministic or stochastic nature of radiation-induced cataracts. It was believed that cataract development is a deterministic effect which has a dose threshold of 0.5 – 2.0 Gy for acute exposure and of 5.0 Gy for protracted or fractionated exposure . A recent study (3) found a statistically significant dose-response increase in the prevalence of cataracts with a threshold dose of 0.6 Sv After the Chernobyl accident a prospective study of the cohort of 8,607 Chernobyl clean-up workers at 12 and 14 years after the exposure (median lens dose 0.12 Gy) revealed a statistically significant odds ratios (OR) per 1 Gy of lens dose were found for stage 1 superficial posterior cortical changes, for early posterior subcapsular changes and for stage 1 posterior subcapsular changes (4). The dose thresholds were within the range of 0.3 – 0.5 Gy which is a much lower threshold than was accepted previously.

Objectives

- To confirm the observed risk in developing radiogenic cataracts in Chernobyl liquidators;
- To estimate the value for dose threshold, in particular for higher grade cataracts;
- To clarify if some fraction of radiation-associated Grade I opacities progress to become more severe, vision-disabling.

Justification

As a number of studies on cataracts conducted at the low-to-medium-dose range is limited and a controversy exists about deterministic or stochastic nature of the radiation-induced cataracts, it makes it important to continue investigation of radiation-induced cataracts following the Chernobyl accident. Results of the previously performed studies (4) indicated that cataracts arising in the population of Chernobyl liquidators, corrected for the most important confounding factors, were related to the dose received. For the most part, the doses were less than 0.5 Gy of low-LET radiation acquired in a protracted/fractionated manner. A key finding was that the data were not compatible with a dose-effect threshold of more than 0.7 Gy.
Studies of Chernobyl liquidators therefore provide a unique opportunity to assess the risk of the radiation induced cataracts following exposure to low doses, to find out about magnitude of such risk, about rate of progression from early lens lesion to more advanced visual-impairing lesions, to evaluate possible threshold following the exposure at a wide range of doses, with dose to the lens to be within low-to-medium range. The duration of the follow-up of 23 years is sufficient for detecting a time since exposure effect on cataract occurrence.

Proposal

The feasibility of a prospective cohort study of Chernobyl liquidators has already been demonstrated in UACOS study. This proposal is to extend the study of radiation induced cataracts in the cohort of Ukrainian liquidators using already existing infrastructure and approaches in order to prevent its collapse.

Study approach

The prospective Ukrainian/American Chernobyl Ocular Study (UACOS) was set up in the 90's. The cohort consists of 8,607 liquidators who have undergone two rounds of ophthalmological examinations. The existing structure can be used to continue following this population for further development of lenticular changes.
In the UACOS, staff are well-trained and experienced, development of the dose reconstruction method is well advanced, two rounds of the ophthalmological examinations have been completed and there is potential risk that delay in conducting the next screening round will cause problems in loss of the staff and in retrospective validation of ophthalmological findings.
The liquidators should be examined at regular intervals for manifestations of possible radiation effects on the lens. Ophthalmological examinations should be performed by trained staff using the same technique and uniform evaluation and staging criteria. The results of ophthalmologic examination of the lens should be documented (photographed) to allow a panel of international experts to verify cataract diagnoses.
Individual questionnaires should be distributed to obtain information on other risk factors for cataracts.

Dosimetry

Considerable efforts have been made to assess doses to the lens within the UACOS study. The median estimated lens dose for the cohort was 123 mGy, while 4.4% of the cohort members received dose >500 mGy. Although bias corrections and uncertainty estimates based on available information were applied in this study and for each individual the uncertainty distributions were randomly sampled to estimate his/her summed γ-ray and β-particle dose, the dose estimation is still a work in progress. There may have been some underestimation of uncertainties, and correlated uncertainties were not modeled as such. Obtaining detailed information on work locations for the workers should also increase the validity of the dose estimates.

Next steps

- The principle investigators of UACOS study should submit a proposal detailing the support (logistic and political) needed to launch the third round of ophthalmological examinations

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Proposal 6 – preparatory or feasibility work required

Cardiovascular and Cerebrovascular Diseases

Background

The significant burden from diseases relating to the circulatory system represents a major population health concern and a challenge for public health risk management in many countries world wide. High (radiotherapy) doses of radiation have also been shown consistently to increase the risk of cardiovascular and cerebrovascular diseases (1;2). In recent years, evidence has also emerged suggesting moderate doses of ionizing radiation can contribute to excess cardiovascular and cerebrovascular disease risks (3). 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.
The risk of cardiovascular and cerebrovascular diseases related to lower doses of radiation has become a topic of substantial concern in radiation protection as the existence of a risk at low doses would challenge the current radiation protection system.

Objective

To determine whether morbidity and mortality from cardiovascular and cerebrovascular diseases are associated with low to moderate doses of ionizing radiation.

Justification

Currently, there is great uncertainty regarding the effects of low to moderate doses on cardiovascular and cerebrovascular diseases risks. The Chernobyl exposed populations – particularly the liquidators and possibly the evacuees – 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. Knowledge to be gained from analyses of data from Chernobyl will be invaluable for radiation protection.

Proposal

While the feasibility of conducting nested case-control studies of specific cancer types within cohorts of liquidators has been successfully shown and such studies have been conducted, concerns remain about the feasibility of studies of non-cancer diseases because of the much larger number of hospital departments that need to take part in such studies and because of possible difficulties and inconsistencies in diagnoses.
In preparation for a case-control study of cardiovascular and cerebrovascular diseases among liquidators, to conduct pilot work to ensure the logistical feasibility of ascertaining and verifying cases.

Proposed Approach

The most informative population would likely be the Chernobyl liquidators included in the Chernobyl registries of the Russian Federation, Belarus, Baltic countries and Ukraine who participated in the clean-up activities in 1986-87 in the 30-km zone (see section on "life-span" cohort for a description of the population). This is one of the best defined populations of exposed persons, with the highest average whole body dose levels. The large size of this population allows for identification of large numbers of cases and

hence ensures statistical power. Given that a cohort of liquidators has been enumerated, focusing on this population would be most fruitful.
The pilot work necessary would focus on identifying and contacting relevant hospital departments in several regions to ascertain sources of cases, verify available information and discuss and test methods for identifying cases and validating diagnoses.

Dosimetry

Dose-reconstruction to a number of specific organs (red bone marrow and thyroid) from external radiation and from intake of long-lived radionuclides has been successfully conducted in nested case-control studies of liquidators using Realistic Analytical Dose Reconstruction with Uncertainty Estimation (RADRUE) (4). RADRUE can also be used to estimate doses to other organs from these radiation types. Although, due to the detailed information needed and to the labor intensive process, RADRUE could not be used to estimate individual doses to very large cohorts, it is feasible to use it in a nested case-control or case-cohort study.

Next steps

The pilot proposal should

- Establish a small steering committee of relevant specialists
- Identify and contact relevant hospital departments in several regions
- Ascertain all sources of cases
- Verify available information
- Test methods for identifying cases and validating diagnoses.

Reference List

(1) 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):256-7.

(2) Hancock SL, Tucker MA, Hoppe R.T. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA 1993;270(16):1949-55.

(3) 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.

(4) Kryuchkov V, Chumak V, Maceika E, Anspaugh LR, Cardis E, Bakhanova E, et al. Radrue method for reconstruction of external photon doses for chernobyl liquidators in epidemiological studies. Health Phys 2009;97(4):275-98.

Proposal 7– preparatory or feasibility work required

I. Chernobyl Life Span Cohort

1) Cohorts of Chernobyl liquidators

Background

Cohorts of liquidators 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 in 1986 and 1987, when doses were highest, at the reactor site and the surrounding 30 km zone (1). 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 to radiation from the Chernobyl accident (2;3).

Objective

- To establish and commit to the long-term follow-up of this well-defined cohort which can be the basis for studies of the long-term health consequences of the accident.

Justification

This cohort would be invaluable in contributing new knowledge on the effects of low to moderate doses on a number of health outcomes of interest (including cancer and non-cancer outcomes, such as cardiovascular and cerebrovascular diseases). It is a large cohort with a wide range of low to moderate doses and as such it is the population of persons exposed to radiation after Chernobyl which is likely to be most informative, with the greatest statistical power, for the study of cancer and non-cancer effects.

Proposal

We recommend that registries of liquidators be maintained as accurately and completely as feasible and the data across countries be harmonized. Data from these registries would be invaluable to future studies in identifying eligible study subjects and ascertaining outcomes of study interests.

Study approach

We recognize that this cohort is too large to be followed-up actively in its entirety and, given difficulties with population registration in the most affected countries, even a complete passive follow-up poses a major challenge. We also recognize that it may not be possible to calculate individual doses for everyone and collecting information on potential confounders and modifying factors would not be feasible for the whole cohort.
However, future case-cohort or case-control studies nested within this cohort would be a viable and powerful epidemiological tool for the study of radiation risk in this cohort. Accurate maintenance of the cohort rosters would allow for unbiased recruitment of cases and controls for studies of specific outcomes of interest.

Dosimetry

Dose-reconstruction to a number of specific organs (red bone marrow and thyroid) from external radiation and from intake of long-lived radionuclides has been successfully conducted in nested case-control studies of liquidators using Realistic Analytical Dose Reconstruction with Uncertainty Estimation (RADRUE). This approach could also be used to estimate doses to other organs from these radiation types. A foreseeable challenge is the future ability to continue doses reconstruction efforts using highly specialized techniques such as RADRUE given that the experts are getting older.
On a broader level, official doses estimates exist in the Chernobyl Registries for a large number of liquidators. For full cohort follow-up, it is important that these doses be validated and that the feasibility of improving them and quantifying uncertainties be ascertained.

Feasibility

The feasibility of conducting nested case-control studies of specific outcomes within cohorts of Chernobyl liquidators has already been demonstrated. The challenge in each study would be to define procedures for identifying the cases in a complete and comprehensive way. Difficulties in collecting reliable information on potential confounding or effect modifying factors 23 years or more after the accident would also need to be addressed.
The feasibility of conducting full cohort follow-up in each country depends on the country. An essential aspect will be the improvement of official dose estimates across cohorts.

Next steps

The pilot project should

- Arrange a meeting of staff responsible for maintaining Chernobyl registries to review comparability of information and feasibility of harmonising data collected and approaches
- Establish a trans-national steering committee to overview harmonisation, plan joint studies and review proposals from other groups for use of data
- Arrange a meeting of dosimetrists to review adequacy of available dose estimates and feasibility of improving them.

Reference List

(1) 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):127-40.

(2) Kesminiene A, Evrard AS, Ivanov VC, Malakhova IV, Kurtinaitis J, Stengrevics A, et al. Risk of Hematological Malignancies among Chernobyl Liquidators. Radiation Research 2008;170:721-35.

(3) 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;170:711-20.

2) Cohorts of children with measured thyroid activity

Background

Two specific 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 the most contaminated regions (oblasts) of these countries 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 include about 15,000 subjects from Belarus and the same number 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. They have been periodically screened for thyroid disease with ultrasound examination and palpation since 1998 and have provided valuable information on thyroid cancer and thyroid disease risk. The NCI is now discontinuing support for the active follow-up of the Bel-Am and Ukr-Am cohorts and only passive follow-up through cancer and mortality registries are planned.

Objective

To establish and commit to the long-term follow-up of these populations which can be the basis for studies of the long-term biological and health consequences of the accident.

Justification

This is a well defined cohort of 25,000-30,000 children from Belarus and the Ukraine exposed to radiation emitted from the Chernobyl accident. By design, it includes a large proportion of children from the most contaminated territories. It is rich in information necessary to study all types of thyroid diseases including, but not limited to, thyroid cancer. Active follow-up conducted in the past included systematic collection of blood and urine samples, thyroid palpation, ultrasound examinations to determine structural abnormalities of the thyroid, medical history and analysis of thyroid hormone levels.
The existence of this cohort makes it a unique source of information not only for the study of thyroid diseases but also for a number of other outcomes for which screening is needed in a well-defined population with individual dose estimates. It would also be invaluable for the conduct of clinical and health services research.

Proposal

The potential for scientific contribution from this cohort to the radiation literature is very important. As such, it is proposed that an EC initiative should seek to join forces with the data custodians of this cohort in order to continue active screening of this population.

Study approach

Since there are other pressing research questions that could be addressed using data collected by this cohort, we would suggest continuing the active screening of the population, but broadening the scope of the studies - looking not only at thyroid diseases but at a range of other diseases for which this population will be informative (including cataracts, etc.).

Dosimetry

Thyroid doses have been estimated for all subjects from 131I and are underway for external radiation and intake of long-lived radionuclides. The approach used for reconstructing doses from the later sources should be applicable to the estimation of dose to other organs of interest.

Feasibility

The feasibility of conducting periodic active screening of this cohort has been demonstrated.
Political boundaries may present an obstacle for collaborative efforts like the one proposed here. These cohorts have been set-up and followed-up under the framework of bilateral agreements with the US and negotiations will be required to explore the potential for possible collaborations.

Next steps

- Official EC contact with the data custodians of this cohort in order to continue active screening of this population.
- If agreement is reached, establishment of a trans-national steering committee to overview harmonisation, plan joint studies and review proposals from other groups for use of data

Reference List

(1) Stezhko VA, Buglova EE, Danilova LI, Drozd VM, Krysenko NA, Lesnikova NR, et al. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: objectives, design and methods. Radiat Res 2004;161(4):481-92.

3) Evacuees and Offspring of Liquidators and Evacuees

Background

In the days after the Chernobyl accident, approximately 116,000 residents living within the 30 km exclusion zone were evacuated. Over 100,000 residents of contaminated territories of Belarus and Ukraine were also relocated in the following months. Whole body doses to the evacuees are estimated to be of the order of 33 mSv on average (1) making this, the second most exposed population after the liquidators.
Since then, several tens of thousand children have been born to families of evacuees and of liquidators. About 43,500 are currently registered in the Chernobyl Registries of Russia and Belarus.

Objective

To establish and commit to the long-term follow-up of:
- a well defined cohort of evacuees
- a well defined cohort of offspring of those most exposed as a results of the accident (liquidators and evacuees)

that can be the basis for studies of the long-term biological and health consequences of the accident.

Justification

Of all of the populations exposed to radiation from the accident, the liquidators and evacuees are those with the highest average doses and the widest dose distributions. Many of them are, in principle, registered in the Chernobyl registries, making it theoretically possible to reconstruct rosters of these populations. The offspring of liquidators and evacuees is a particular important source of information on effects of pre-conception and in-utero exposure to radiation.

Proposal

Given the potential amount of information that could be obtained for radiation protection from studies of these populations, it is proposed that the feasibility of assembling these cohorts be assessed.
The feasibility study should focus on the feasibility of establishing representative rosters of the populations, of tracing them 23 years after the accident and of reconstructing individual doses.

Study approach

A pilot study should be conducted to evaluate the completeness of available sources (Chernobyl registries, lists of Ministries of Internal Affairs, or of Chernobyl or Emergency Affairs ministries, depending on the country) needed to identify and trace potential study subjects and the feasibility of reconstructing individual doses. This study would be helpful in determining whether future studies based on these cohorts would be logistically possible and informative.

Dosimetry

The feasibility of reconstructing individual doses to evacuees, as well as in utero and postnatal doses of offspring of liquidators and evacuees need to be evaluated.

Feasibility

Data on evacuees and on offspring of liquidators and evacuees are difficult to obtain, and there is anecdotal evidence that, following their relocation, many of the evacuees have subsequently moved and that official registration of their movements does not exist.
The feasibility lf setting up and following up these cohorts therefore needs to be assessed.

Next steps

The pilot study should arrange

- Meeting of staff responsible for maintaining Chernobyl registries to review information registered on evacuees and offspring of liquidators and evacuees.
- Establishment and conduct of a formal feasibility study.
- Meeting of dosimetrists to review existing dose estimates and feasibility of reconstructing doses for entire cohorts.

Reference List

(1) 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):127-40.

II. Tissue banks

Background

The value of storing samples of tumour tissue and paired samples of non-neoplastic tissue or blood, either as intact samples or as nucleic acid extracts is widely recognised(1-5). The samples allow study of both somatic and germline changes involved in the carcinogenetic process, and allow the application in the future of techniques yet to be developed which may enable answers to some of the basic questions in carcinogenesis, including radiation carcinogenesis. Storage of such samples is particularly important for major radiation events where large numbers of radiation related tumours occur with a known latency and where both the molecular evolution of the tumours and the molecular epidemiology need study..

The possibility of creating a tissue bank specifically for the Chernobyl related projects that may result from the ARCH strategic review, of encouraging each project to store its own samples, or of collaboration with the existing Chernobyl Tissue Bank(6) was discussed by the ARCH expert group. The need to store samples of tumour and blood or buccal mucosa was widely supported, but before deciding on any proposal for the strategic research agenda it was considered that more information was needed on the existence, number, content, and distribution of tumour/tissue banks in the three most affected countries.

Proposal

Creation of a simple questionnaire seeking information on existing tissue banks in the three most affected countries. Circulation to appropriate members of the expert group, together with a request that copies be passed to other centres involved in tissue storage. These would include the major centres involved in treating thyroid cancer, and others dealing with large populations from exposed areas, treating conditions such as breast cancer. Analysis of the responses so that the information can then be used for decision on the proposals in the SRA.

Reference List

(1) Cambon-Thomsen A. The social and ethical issues of post-genomic human biobanks. Nat Rev Genet 2004;5(11):866-73.

(2) Davey-Smith G., Ebrahim S, Lewis S, Hansell AL, Palmer LJ, Burton PR. Genetic epidemiology and public health: hope, hype, and future prospects. Lancet 2005;366(9495):1484-98.

(3) Oosterhuis JW, Coebergh JW, van Veen EB. Tumour banks: well-guarded treasures in the interest of patients. Nat Rev Cancer 2003;3(1):73-7.

(4) Riegman PH, Morente MM, Betsou F, de BP, Geary P. Biobanking for better healthcare. Mol Oncol 2008;2(3):213-22.

(5) Wild CP. Environmental exposure measurement in cancer epidemiology. Mutagenesis 2009;24(2):117-25.

(6) Thomas GA, Williams ED. Thyroid tumor banks. Science 2000;289(5488):2283.

Annex A

Criteria for classification of projects

In deciding the urgency of projects, the importance, practicability and resource requirements should be taken into account.

Urgent high priority projects

These should include one or more of the following:

A) Work of major scientific or social importance, which if funded could start without undue delay.

B) Valuable work in progress which would collapse without urgent support.

C) Infrastructure forming an important resource for current and/or future projects, including those requiring urgent political discussion rather than short term financial support

It was recognised that in addition to the above and to the longer term priority projects that will be included in the Strategic Research Agenda as part of WP2, there were projects of scientific and/or social importance which would be difficult to start without further work on the practicability or infrastructure needed.

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