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The Chernobyl Tissue Bank (CTB)

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Final report
(summary)

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Generic research in radiological sciences

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Introduction

The Chernobyl accident happened on 26 April 1986, when an experiment went disastrously wrong. The resultant explosion and fire in the graphite core led to the release of more than 10^{19} becquerel (Bq) of radioisotopes including 1.8 x 10^{18} Bq of 131-iodine, 2.5 x 10^{18} 133-iodine, and 1.1 x 10^{18} 132-tellurium, which decays to 132-iodine. It was the largest release of radioiodine into the environment and the radiation exposure of the population was quite different from that of the atomic bombs in Japan. In Japan, many people were killed by the blast from the bomb and those who survived received mainly external radiation. The most pronounced risk of thyroid cancer in those exposed to radiation from the atomic bomb was found in those exposed under the age of 10 years and the highest risk 15-29 years after exposure; an increased risk was still present 40 years after exposure. The routes of exposure after the Chernobyl accident were largely those of inhalation or ingestion of radionuclides. The thyroid is the only organ in the body to concentrate and bind iodine; exposure to the thyroid from 131-iodine is 1000-2000 times the average body dose.

Whilst having serious consequences for the population, particularly those who were children at the time of the accident, in the immediate vicinity of the power station and those exposed to high levels of radiation from the fallout, the Chernobyl accident provides a unique opportunity to collect samples of a human cancer, with a low natural incidence, for which both the aetiology and the time of exposure to the etiological agent is known. Thyroid cancer is normally rare in children, of the order of 1 per million per year, although there is 50 % variation in this figure across the globe. It is therefore likely that the majority of the thyroid cancers that have arisen in this population are a direct consequence of exposure to radioiodine in fallout.

The Chernobyl Tissue Bank (CTB) is an internationally supported project, with funding provided by four sponsors (the European Commission (EC), the National Cancer Institute of the US (NCI), the Sasakawa Memorial Health Foundation of Japan (SMHF), and the World Health Organization) and support provided by two countries most affected by fallout from the reactor accident, Ukraine and the Russian Federation. A number of projects studying the effect of the Chernobyl accident were funded by the four sponsors listed above in the early 1990s. The increase in Belarus and Ukraine was confirmed in a number of publications. By 1995 it was becoming apparent that several European research groups were unknowingly receiving material from the same patients for research, and that there were discrepancies in the pathological diagnoses being applied to the same tumour. Subsequently, a report to the EC confirmed that there had indeed been considerable overlap since 1995 among a number of EC-funded molecular biology projects. It was then recognised that a cooperative tissue bank would reduce the duplication of research effort and provide better scientific data on the health effects of the Chernobyl accident. A meeting was held between senior members of the European Thyroid Association (Professors Dillwyn Williams and A. Pinchera) the American Thyroid Association (Professors Jacob Robbins and David Becker) and the Asia-Oceanic Thyroid Association (Professor S. Nagataki) to devise a strategy for funding an international project. Negotiations took place among the four funding partners in 1996-1997 and once the funders had reached agreement on an appropriate framework, additional negotiations took place in 1997-1998 with representatives of the Ministries of Health of Belarus, Ukraine and Russia. Applications were made for financial support from the four funding agencies, with the first funds being made available from the EC in January 1998 for the development of protocols for collection and documentation of specimens. Following agreement on the various protocols, the project officially started collecting material on 1 October 1998. Although the

project was initially coordinated from the University of Cambridge, UK, the coordinating centre moved to the University of Wales, Swansea, in 1992 following the appointment of Professor Gerry Thomas, the Principal Investigator and Project Manager to a senior lectureship at the new Swansea Clinical School. A western European coordinating centre, able to hold grants from each of the four sponsors, is central to the financial and administrative management of the project.

Objectives

The main objective of this project is to provide a research resource for both ongoing and future studies of the health consequences of the Chernobyl accident. It seeks to maximise the amount of information obtained from small pieces of tumour by providing multiple aliquots of RNA and DNA extracted from well-documented pathological specimens to a number of researchers worldwide and to conserve this valuable material for future generations of scientists. It exists to promote collaborative, rather than competitive, research on a limited biological resource. The project aims to:

- collect and curate biological specimens with appropriate consent from patients operated for thyroid cancer or cellular follicular adenoma and who were born on or after 26 April 1967 (i.e. aged 19 or under at the time of the Chernobyl accident)
- provide quality-assured materials (both in terms of pathology and molecular biology) to the wider research community
- provide a database to the wider research community that links dosimetry data with information on age at clinical presentation and at the accident, residency and pathology of tumour
- provide a web-accessible data warehouse for future research investigation on data assembled from research projects funded by the EC, NCI and other sponsors.

Continued collection of material is necessary for a number of reasons. There is evidence that suggests that tumours following a short latency are likely to show a different molecular biological and pathological profile than those of a longer latency. This project will help to clarify this difference as the latent period since the accident increases. Thyroid cancer is increasing worldwide and although most tumours do not have a defined radiation aetiology, it is likely that the insights gained from studying the post-Chernobyl tumours will provide information that could be of use to thyroid (and other) cancers in general.

In addition to the continued focus on the first three aims listed above, progress has reached the point where the fourth aim is an increasingly important objective. The majority of cancer research projects obtain material from different patients whose disease may be of differing aetiologies. Frequently the pathological detail of the type of tumour under study is scanty, different pathologists may provide different opinions on the same tumour and different molecular biological techniques are used, making accurate comparison between different studies difficult. This project allows multiple researchers access to the same material, permitting comparison of different techniques for the same molecular marker, as well as analysis of multiple molecular markers. In addition, it provides the opportunity for additional markers (some of which may not yet have been discovered) to be studied at later time points. A number of similar projects to amass biological archives from specific patient groups exist. However, few of these projects seek, from their outset, to collate research data produced from the samples collected. This archive is different in that it deals with a relatively rare tumour

whose aetiology is known, therefore enabling study of the interaction of environment and physiology in the development of a particular cancer.

Results

Bio specimens from the CTB have been provided to the major research groups involved in the studies of the consequences of the Chernobyl accident, many of which are in receipt of EC funding. This approach provides a basis that fosters international collaboration and reduces the chance of competition and even friction between groups in their requests for this material. Researchers who obtain material from the resource agree to provide the results of their investigation on a case-by-case basis to enable combined analysis carried out at a later date. The provision of extracted nucleic acid from thyroid tissue, rather than each researcher being provided with a small piece of tissue, maximises the amount of data that can potentially be obtained from a single operative specimen and enables multiple molecular biological studies to be carried out for each case.

To date, 1778 cases of thyroid cancer and adenoma have been so far reviewed by the pathology panel from Ukraine and Russia. 1463 of the 1778 reviewed cases have frozen tissue available, the majority of these are paired tumour-normal samples; some have metastatic tissue. Of the 1778 cases, 1385 are from the exposed areas of Ukraine and Russia. 393 cases come from the unexposed oblasts of Ukraine and Russia. There are 222 post-Chernobyl cases (born after 1 December 1986) from Ukraine and Russia: 138 cases are from the exposed areas and a further 84 are from unexposed areas. 1596 aliquots of RNA and 585 aliquots of DNA from tissue have been so far released. 131 aliquots of DNA from blood and 6595 sections from formalin-fixed paraffin-embedded tissue have been issued. Details of the publications resulting from material supplied by the project are listed on the project website (www.chernobyltissuebank.com).

The most important scientific findings that have emerged from this project have been the demonstration that the age of the patient at diagnosis has more effect on the molecular biology of the tumour than the aetiology of the tumour. These findings have discredited the early reports that rearrangement of a specific oncogene, the ret oncogene, was related to radiation exposure. The association with a specific type of ret rearrangement is now known to be related to a specific subtype of papillary carcinoma that is more common in younger patients. This work has been further supported by the lack of demonstration of involvement of the BRAF oncogene in the classical subtype if papillary thyroid cancer in children, irrespective of its association with radiation exposure. Conversely, BRAF is commonly mutated in the classical type of papillary carcinomas in adult patients. These findings have led to a re-think of the hypotheses that surround the generation of papillary thyroid cancer and a realisation that the interaction of cellular pathways both within a cell and in its interaction with the surrounding tissue may alter with physiological features that change with age. In addition, a recent finding that another type of carcinoma of the thyroid follicular cell, follicular carcinoma, may also be now rising, suggests that longer-term studies will be required to assess the full risk of development of thyroid cancer following radiation exposure.

The CTB has been the paradigm for a number of other tissue banks, and complies with the best practices for tissue banking as outlined by the National Cancer Institute of the US (http://biospecimens.cancer.gov/biorepositories) and by the Human Tissue Authority of the UK (www.hta.gov.uk/guidance/codes_of_practice.cfm).

Implications

The majority of thyroid cancers that have occurred in the affected population post Chernobyl have been papillary carcinoma, and the majority of these have been of one subtype, associated with a particular molecular biology. However, a recent review of the data available from the CTB in combination with that available from earlier projects suggests that different pathological types of thyroid cancer may arise in a radiation-exposed population with differing latencies. It is now highly likely that there are a series of cohorts of exposed individuals, with differing levels of risk, influenced by their age at exposure, who may develop different types of thyroid cancer with differing latencies. Continued detailed monitoring is therefore the only way to provide accurate information for assessment of risk to a population from another reactor accident. The findings on the altered patterns of molecular pathology with age at diagnosis are not peculiar to thyroid cancer – it is also supported by recent studies in breast, gastric cancer and leukaemia.