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Gene-radiation interactions: their influence on pre-menopausal breast cancer risk after Chernobyl

(GENE-RAD-INTERACT)

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Final report
(summary)

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Project coordinator

International Agency for Research on Cancer (IARC), FR

Project partners

Finnish Cancer Registry (FCR), FI

Belarus Centre for Medical Technologies, Information, Computer Systems, Health Care (BelCMT), BY

Ukrainian Cancer Registry (UCR), UA

Subcontractors:

Institute of Biophysics (IBP), RU

Radiation Protection Institute (RPI), UA

Objectives

Breast cancer is the most common cancer and one of the leading causes of death from cancer among women worldwide, with nearly 1 000 000 new cases per year (Globocan, 2000). Known risk factors for breast cancer include genetic susceptibility, reproductive factors, post-menopausal weight, history of benign breast disease, and exposure to ionising radiation (UNSCEAR 2000, Stewart and Kleihues, 2003).

Epidemiological studies of atomic bomb survivors and medically irradiated populations show increased risks of female breast cancer (ranging from 1.1 to 2.7 at 1 Gy) following external irradiation before the age of 40 years (Boice et al., 1996). The relative risks of breast cancer for women exposed to external radiation in childhood and adolescence are substantially higher than for those exposed as adults (Bhatia et al., 1996, Hildreth et al., 1989, Pierce et al., 1996, Thompson et al., 1994, van Leeuwen et al., 2000, van Leeuwen et al., 2003) and are among the highest known radiation-related risks for any cancer type along with leukaemia and thyroid cancer following exposure in childhood (UNSCEAR, 2000).

A number of studies have clearly demonstrated that a fraction (of the order of 12 %) of breast cancer risk is inherited (Goldgar et al. 1994; Lichtenstein et al. 2000; Pharoah et al. 2002; Amundadottir et al. 2004). Several of the genes that play important roles in the response to DNA damage produced by ionising radiation are now implicated as either high-risk or moderate-risk breast cancer susceptibility genes. These include *BRCA1*, *BRCA2*, *ATM, NBS1, CHEK2, XRCC1* and *XRCC3*. It is therefore of interest to evaluate the possible joint roles of ionising radiation and genetic susceptibility in the risk of breast cancer.

In 1986, the Chernobyl accident resulted in radioactive contamination of large areas of Belarus and Ukraine and substantial doses to hundreds of thousands of persons in the most contaminated areas. Increases in the incidence of breast cancer incidence in young women reported in Belarus and Ukraine recently are not unexpected since in the most contaminated districts of these countries (situated in the Gomel, Mogilev, Zhitomir, Chernigov, and Kiev regions), the average lifetime radiation doses to the breast from external radiation and intake of long-lived isotopes (in particular ^{137}Cs) are of the order of 100 mSv (UNSCEAR, 2000).

The observed increase in the incidence of breast cancer in the contaminated areas of Belarus and Ukraine has become an issue of public concern and the role of radiation and other factors needs to be assessed. The objectives of the project were therefore to:

- explore whether the observed increase in pre-menopausal breast cancer incidence is likely to be related to radiation exposure;
- assess the feasibility of carrying out a population-based case-control study to evaluate the possible interaction between radiation exposure and possible modifying factors, including age at exposure and genes that are known to influence radiation sensitivity and the risk of breast cancer development.

Brief description of the research performed and methods/approach adopted

The work carried out in the current project consisted of three closely interrelated work packages, designed to achieve the objectives listed above.

WP 1 – Descriptive epidemiology of pre-menopausal breast cancer since the Chernobyl accident in contaminated areas of Belarus and Ukraine

WP 2 – Assessment of the feasibility, setting up mechanisms, and testing procedures for carrying out a case-control study to examine gene interactions in radiation-induced pre-menopausal breast cancer

WP 3 – Development and testing of dose reconstruction method.

Work under these work packages involved:

- carrying out a full descriptive epidemiological analysis of breast cancer incidence in Belarus and Ukraine, focusing on age-cohort-period-region analyses to evaluate whether increases in pre-menopausal breast cancer incidence in Belarus and Ukraine seen since 1986 are related to radiation exposure from the Chernobyl accident
- evaluating formally the mechanisms necessary to carry out a population-based case-control study of breast cancer in the regions (oblasts) of Gomel and Mogilev in Belarus and of Kiev, Zhitomir and Chernigov in Ukraine
- testing the procedures for collecting and analysing relevant biological samples (blood and human tissue) to be used within the case-control study to assess molecular alterations in breast cancer susceptibility genes
- developing a common dosimetry approach for reconstruction of individual doses for both cases and controls for a possible future case-control study. Both external and internal exposure pathways were considered. Within this project, work focused on: (a) identification of existing models for dose estimation; (b) critical review of these models; (c) testing of the models by comparing predictions to doses available from instrumental data; (d) development of a dosimetry questionnaire; (e) outlining and development of a dosimetric model for individual dose reconstruction for subjects in a possible epidemiological study in Ukraine and Belarus
- developing and testing all study documents for a future population-based case-control study and establishment of the necessary collaborations in the field.

Main achievements

All of the objectives of the project have been achieved during the contract period.

Results of the descriptive epidemiological study (Work Package 1) indicate that the observed increase in breast cancer incidence in young women in the most contaminated areas of Belarus and Ukraine is real and that a dose-related increase is seen among women who resided in the most contaminated regions (with average cumulative doses of 40 mSv or more). Significantly increased relative risks of the order of 3-4 have been found since 1998 among women exposed before the age of 45 in the most contaminated regions compared to less contaminated territories. These observations do not appear to be due to screening, as similar results are obtained for symptomatic breast cancer, as well as for both localised and non-localised tumours.

These results therefore suggest that the conduct of a population-based case-control study in these regions would be of value in precisely evaluating the role of radiation and of possible modifying factors in the observed increased incidence in young women.

Work Package 2 was designed to evaluate the feasibility and the most effective and efficient mechanisms and procedures for a case-control study designed to assess the role of radiation and its interaction with breast cancer susceptibility genes in the risk of breast cancer in young women in the contaminated regions of Belarus and Ukraine. The feasibility study carried out has demonstrated that a population-based case-control study of breast cancer in young women in these areas is both feasible and informative as the statistical power to study radiation effects and possible interactions with genetic predispositions is good.

Work Package 3 focused on the assessment of the feasibility of reconstructing individual radiation doses for the purpose of a possible case-control study. Existing dose reconstruction models were critically reviewed, tested, and modified and common approach developed. The proposed methods take into account the following exposure pathways: external exposure from gamma-emitting radionuclides deposited on the ground; internal exposure from inhalation (mainly for the evacuated populations); internal exposure from short-lived radioiodines (for specific subgroups of population, in particular lactating women); internal exposure from ingestion of long-lived isotopes (mainly caesium).

As a result of the work under this contract, all steps have been completed for the implementation of a population-based case-control study to further clarify the role of ionising radiation in the observed increase in breast cancer risk in young women in contaminated territories of Belarus and Ukraine. This includes the preparation of the study protocol, questionnaire, and procedures and of the operations manual for dose reconstruction.

Funds now need be sought for the conduct of this study, which should provide important information for radiological protection in Europe and elsewhere, improve our understanding of mechanisms of radiation-induced cancer, and provide information to local authorities in the countries affected by the Chernobyl accident about the magnitude of the radiation effects.

Exploitation and dissemination

Results of the work under Work Packages 1 and 3 will shortly be submitted for publication in the peer-reviewed scientific literature and will be the subject of scientific presentations at meetings.

The outcome of Work Package 2 is the development of a study protocol, procedures, and a questionnaire as well as the establishment of the necessary collaborations to ensure a smooth implementation of the study. Exploitation of these outcomes will mean their use in an actual population-based case-control study in the contaminated regions of Belarus and Ukraine. The conduct of such a study is justified by our findings and funds are being sought for its implementation and conduct.