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BELARUSIAN *IN UTERO* COHORT: NEW OPPORTUNITY TO EVALUATE HEALTH EFFECTS OF PRENATAL AND EARLY-LIFE EXPOSURE TO IONIZING RADIATION

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Abstract

In April 1986, the Chernobyl nuclear accident resulted in wide-scale contamination of Belarus with significantly elevated levels of radioiodine isotopes, mainly Iodine-131 (^{131}I), and long-lived radiocesium isotopes, mainly Cesium-137 (^{137}Cs). Various groups of the population were affected by exposure to ionizing radiation, including pregnant women and their fetuses. This paper describes the methods and results related to establishment of a cohort of 2,965 Belarusian persons exposed *in utero* due to Chernobyl fallout. The cohort consists of individuals whose mothers resided in the most radioactively contaminated areas in Belarus at the time of the accident. Prenatal and postnatal doses to the thyroid due to intake of ^{131}I, external irradiation and ingestion of radiocaesium isotopes were estimated for all cohort members. Ongoing research on this unique cohort will provide important information on adverse health effects following prenatal and postnatal exposure to radioiodine and radiocesium isotopes, for which available epidemiological data are scant.

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Supplementary Information. Appendix 1. The study questionnaire. Appendix 2. Power calculations.

1. Introduction

The accident at the Chernobyl nuclear power plant in April 1986 resulted in massive releases of radioactive materials into the atmosphere and contaminated large areas of Ukraine and Belarus with significantly elevated levels of radioiodine isotopes, most importantly ^{131}I, which remained in the environment for approximately two months after the accident; other radionuclides, especially ^{137}Cs, will remain in the environment, though at a diminishing level, for decades. Among the most vulnerable population groups affected by accident emissions were young children, who consumed large quantities of ^{131}I-contaminated milk. Studies of approximately 25,000 children and adolescents in Ukraine and Belarus exposed to radioactive fallout – the Ukrainian-American (UkrAm) and Belarusian-American (BelAm) cohorts – have demonstrated increased risk of thyroid cancer and other thyroid diseases associated with exposure to ^{131}I (Brenner *et al* 2011; Cahoon *et al* 2017; Ostroumova *et al* 2009, 2013; Tronko *et al* 2006, 2017; Zablotska *et al* 2011, 2015). Results from these and other studies conducted in contaminated areas of Belarus and the Russian Federation (Cardis *et al* 2005; Davis *et al* 2004) strongly suggest elevated risk of thyroid cancer after exposure to ^{131}I during childhood and adolescence.

Much less information is available on risk of thyroid cancer, and other diseases of the thyroid gland, associated with exposure to radioiodine isotopes during the potentially radiosensitive prenatal period. The thyroid gland can be detected in the human embryo at the end of the third week of gestation, and it becomes active around 10–12 weeks of gestation, with the highest thyroid cell proliferation at 11–20 weeks (Saad *et al* 2006). At 10–12 weeks of gestation, the thyroid gland starts to accumulate iodine from the maternal blood via the placental iodine pump (Bidart *et al* 2000). By late gestation fetal radioiodine concentrations may be many times higher than maternal levels (Gorman 1999). The high rate of cellular proliferation, and the very small size of the gland which leads to a high absorbed dose (ICRP 2001), may make the fetal thyroid especially sensitive to adverse effects of radioiodine. To investigate effects of prenatal exposure on the thyroid, a thyroid screening study of about 2,600 subjects exposed *in utero* to radioactive iodine in Ukraine was established in 2002 (Ukraine *in utero* study) in the framework of the Ukrainian-American Thyroid Study. Based on two thyroid screening examinations of *in utero* cohort members, the study found a significantly increased risk of thyroid nodules related to ^{131}I exposure and a marked increase, albeit not statistically significant, in risk of thyroid cancer (Hatch *et al* 2009, 2019).

We have recently constructed a parallel cohort of individuals exposed *in utero* to Chernobyl fallout in Belarus. This paper describes methodological aspects of the new Belarusian *in utero* cohort, including sources of information used for cohort subject recruitment, main characteristics of the cohort, reconstructed radiation doses and cohort follow-up to date.

2. Materials and Methods

2.1. Study Population

The objective of the study fieldwork was to recruit child-mother pairs in which the mother was pregnant at some point between 26 April 1986 and 30 June 1986 – the two-month period in which significant ^{131}I exposure occurred after the accident (Bouville *et al* 2007),

i.e. children who were born between 26 April 1986 and 31 March 1987, and to interview the mothers to obtain information necessary for radiation dose reconstruction and future follow-up. It was decided that the child-mother pairs be sampled from residents who at the time of the accident were in Gomel and Mogilev Oblasts (the two most heavily contaminated areas) and those in some raions of Minsk Oblast and Minsk City (where substantial numbers of residents of the affected areas were known to have resettled shortly after the accident). Oblast is the largest administrative unit in Belarus, similar in size to a province; each oblast consists of smaller administrative units called raions. Study subjects (children) and their mothers had to be alive and reside in Belarus at the time of the first contact beginning in 2012. In addition, mothers had to be residents of the study area at the time of their personal interview.

To search for potential subjects, we used data from multiple source described below, as each source provided only part of the information needed to assemble child-mother pairs. We first merged data on personal identifiers (such as name, date of birth, sex, residence at various points in time) to eliminate overlapping information for ascertaining unique child-mother pairs. After data cleaning and exclusion of duplicate records, a source data file for 6,478 potential unique child-mother pairs was created. The source file was used to locate and trace individuals to confirm their eligibility and arrange for interviews of the mother. The file contained study identification numbers (ID) for the child and their mother, the full names of the child and their mother, the child's date of birth and sex, the mother's date of birth, place of residence at the time of the accident, and the date (or year) of the last known addresses of the child and their mother. The goal was to assemble a cohort of about 3,000 individuals, a size comparable to that of the Ukrainian *in utero* cohort (Hatch *et al* 2009), born in areas of Belarus contaminated by radioiodine isotopes at different levels.

The sources of information used to identify potential subjects were as follows:

1. BelAm cohort study database: The database was constructed based on maternity hospital records and included 86,052 women who delivered live births in the period between 26 April 1986 and 31 January 1987 throughout Belarus. For mothers, the database included full name (last, first and patronymic names), age and address of residence at the time of delivery. For children, only date of birth and sex were available, with no personally identifying information (name). However, these data allowed us to select 11,286 mothers with children who may be potential subjects.

2. Chernobyl State Registry (CSR) of Belarus: This registry contained individual information on all categories of people affected by the Chernobyl accident (liquidators, evacuees, residents of contaminated areas, offspring to exposed parents, etc.). Available information included persons' full name, sex, date of birth, address of residence at last visit to a health care facility, places of residence after the accident. From the CSR we identified 4,770 persons who were born between 26 April 1986 and 31 March 1987, including 467 people born between 1 February and 31 March 1987, time period that was missed at source #1. We also used the CSR to collect missing data (e.g., date of birth) and to verify information on mothers of potential study subjects identified from other sources.

3. Sasakawa Foundation project: A thyroid screening study conducted in Belarus by the Sasakawa Memorial Health Foundation (Ashizawa *et al* 1997) allowed us to access their database, which included recorded thyroid volumes and stable iodine levels in urine measured for 2,358 children in 1991–1996 and for 3,596 children in 1998–2001. We used this database to verify information on study subjects already identified through other sources, i.e., the database of liveborn children of subjects in the BelAm cohort and those identified from the CSR.

In addition, we searched lists of children who graduated from secondary schools in 2003–2004 (i.e. those who were born in 1986–1987) available from archives of public education departments in the most contaminated raions of Gomel Oblast, namely Bragin, Buda-Koshelevo, Vetka, Narovlya, Khoiniki and Chechersk raions (see Fig. 1). We used these lists to update contact information on study subjects and their mothers already identified through other sources.

By compiling data from these various sources, we selected 6,478 potential mother-child pairs (Fig. 2).

2.1.1. Locating potential child-mother pairs—We searched for current addresses of the 6,478 potential child-mother pairs in various sources of information at local authorities, pension funds, and medical facilities in the settlements of the last known address. These organizations/institutions provided information on current residence in the study area, date and place of migration for those who moved out of the study area, or date and place of death, if deceased. We were thus able to establish contact with 4,454 child-mother pairs (68.8%), who would then be followed up for recruitment into the study (see Fig. 2), as described below.

2.1.2. Contacting child-mother pairs for recruitment—We first sent letters of invitation simultaneously to each of the 4,454 child-mother pairs. The letter explained the study purpose, why they were chosen, and the amount of time and burden expected if they agreed to participate in the study, as well as the modest payment to compensate their time and ground transportation cost and provided reassurance regarding their privacy and confidentiality concerns. We asked a potential study subject to sign and return an enclosed informed consent form in a pre-paid enclosed envelope, if they agreed to study participation, and to complete a short questionnaire that included questions on marital status, education, professional group (including hazardous industries) and possible contact with hazardous exposures (e.g., agricultural pesticides, dust, gasoline, ionizing radiation), history of thyroid diseases, smoking habits and alcohol consumption. To each mother, we sent a pre-paid post card specifying the place, date and time of interview, with instructions on how to arrange and confirm an appointment for interview. We also included a list of topics to be covered during the dosimetry/epidemiology interview. This list was intended to help them recall the events that occurred at the time of the Chernobyl accident. To confirm ‘child-mother’ pairs, we asked a potential study subject to provide the full name of their mother, her date of birth and actual address; the same identification information for the subject was requested from the mother.

Mothers were then invited for personal interview after the informed consent had been obtained from their children. A total of 3,138 (70.5%) mothers agreed to participate in the study and be interviewed (Fig. 2); 1,316 pairs could not be included in the study for the following reasons: (i) mother did not meet the study eligibility criteria as she moved into study area after 30 June 1986 (n=314, 7.0%); (ii) potential study subject or mother migrated out of the study area (n=203, 4.6%); (iii) potential study subject or mother was deceased or had serious physical disability (n=463, 10.4%); and (iv) potential study subject or mother refused to participate in the study (n=336, 7.5%).

2.1.3. Personal interview of mother—We conducted personal interviews with mothers using a questionnaire to collect detailed information on behavioral, residential and other information essential for thyroid dose reconstruction. To assist memory recall on milk/dairy product consumption, we used visual probing aids, such as calendar for 26 April – 30 June 1986 with indication of holidays, types and sizes of drinking cup/glass, bottle and container, pictures of dairy products and leafy vegetables. In developing the questionnaire, we held a three-day session in Gomel and Minsk to train interviewers and evaluate/pre-test the draft interview questionnaire; the interviewers conducted interviews strictly following the written manual and practiced interviews with local volunteers who were pregnant at the time of the accident. The feasibility of the questionnaire, which is quite lengthy and detailed, was discussed; problematic/ambiguous questions were identified, and possible solutions were discussed. The final questionnaire, which took 54 to 67 minutes to administer, is divided into 10 thematic sections (Appendix 1). Interviews were conducted at one of the two locations (RRCRM&HE in Gomel or Republican Center for Medical Rehabilitation in Minsk) or by mobile teams of the RRCRM&HE at 10 locations in Gomel Oblast and at 3 locations in Mogilev Oblast. Briefly, the following information was obtained by personal interviews with mothers:

- For mothers: (i) duration of pregnancy (in weeks); (ii) place of residence and construction materials of the house on 26 April 1986, between 26 April and 30 June 1986 (period of exposure to ^{131}I) and between 1 July 1986 and 31 March 1992 (period of exposure to external irradiation and ingestion of radiocesium isotopes only); (iii) consumption of milk, dairy products and leafy vegetables between 26 April and 30 June 1986 (period of exposure to ^{131}I), consumption of milk and dairy products after 30 June 1986 during pregnancy and/ or breastfeeding;
- For children (subjects): consumption of milk and dairy products until the age of five years old.

The questionnaire also included questions for the mother about individual and family history of thyroid diseases, thyroid hormone replacement therapy before or during pregnancy, and, for both the mother and child, about smoking habit.

2.2. Thyroid dosimetry

A detailed description of dosimetry methods and estimated thyroid doses for subjects of the Belarusian *in utero* cohort is given elsewhere (Drozdovitch *et al* 2019). In brief, we estimated (i) prenatal (*in utero*) dose from ^{131}I intake by mother; (ii) for subjects who

were born before 1 July 1986, postnatal dose from ^{131}I intake during infancy via breast milk and other foodstuffs; (iii) prenatal dose from external irradiation from gamma-emitting radionuclides deposited on the ground; (iv) postnatal (until age of 5 years old) dose from external irradiation; (v) prenatal dose from mother's ingestion of foodstuffs contaminated with radiocesium isotopes (^{134}Cs and ^{137}Cs); and (vi) postnatal (until 5 years of age) dose from internal irradiation due to ingestion of foodstuffs contaminated with ^{134}Cs and ^{137}Cs.

Prenatal ^{131}I doses were estimated using individual input data (collected from mother's personal interview) and ecological data (^{131}I ground deposition in the settlements). We used ecological and biokinetic models to reconstruct ^{131}I transportation from ground deposition to the mother's thyroid via the activity intake with contaminated air and foodstuffs calculated using the data on individual behavior and consumption of foodstuffs reported at the personal interview. These models were used to calculate the time-integrated activity of ^{131}I in mother's thyroid and, then, mother's thyroid dose. Estimated thyroid dose for the mother served as input to estimate dose to the fetal thyroid gland using the model from ICRP Publication 88 (ICRP 2001), which accounts for transfer of iodine between the maternal and fetal pools and retention of iodide in the placenta. This model predicts a continuous increase in dose with increasing gestational age, with doses being minimal at early gestation when the fetal thyroid is not yet fully active, and maximal in the third trimester. In addition, 656 cohort member who were born between 26 April and 30 June 1986 were exposed to ^{131}I postnatally; for these subjects, thyroid dose to the infant from ^{131}I intakes via breast-fed milk and other foodstuffs was estimated.

Prenatal and postnatal thyroid doses due to external irradiation were estimated using the model described by Minenko *et al* (2006) that was adapted to make use of the data provided in ICRP Publication 116 (ICRP 2010) for fetal exposure. Exposure from cesium ingestion was assessed using a semi-empirical approach (Minenko *et al* 2006) based on relationship between environmental contamination (^{137}Cs deposition density and ^{137}Cs soil-to-milk transfer) and internal dose due to radiocesium ingestion derived from whole body counter measurements of radiocesium body burden performed in Belarusian population.

2.3 Cohort follow-up

The principal method of cohort follow-up is thyroid screening to ensure systematic ascertainment of cancer and other conditions of the thyroid. The cohort will also be followed up by linkage with the Belarusian Cancer Registry to ascertain a broad range of solid and hematological cancers.

2.3.1 Thyroid screening—Standardized thyroid screening of this cohort follows well-established procedures used in the Belarusian and Ukrainian cohorts of subjects exposed to ^{131}I in childhood and adolescence (Stezhko *et al* 2004), which have also been used for screening of the *in utero* subjects in the Ukrainian cohort (Hatch *et al* 2009; Hatch *et al* 2019). The principal site of thyroid screening will be the RRCRM&HE, Gomel, while mobile teams will be used to screen the subjects who live in areas distant from Gomel.

The initial cycle of thyroid screening examinations began in 2018 and will continue through 2022. Briefly, the screening examination begins with thyroid palpation by an endocrinologist

and ultrasonographic examination by a trained ultrasonographer, followed by a referral to fine needle aspiration biopsy, if indicated, and then to surgery for treatment and histopathological diagnosis. Blood samples are collected for diagnosis of thyroid disorders (e.g., thyroid functional diseases, autoimmune thyroiditis) and for follow-up of thyroid pathology. Samples of whole blood (10 mL) from the study subjects are also frozen for potential future genomic studies.

2.3.2 Cancer registry linkage—Linkage of cohort subjects with the Belarusian Cancer Registry (BCR) is established based on subjects' full name (last name, first name, and patronymic name), date of birth (year, month and day), sex and last known oblast of residence. The BCR is a nation-wide population-based cancer registry in operation since 1978 (IARC 2014). In 1991 the registry system was computerized, allowing electronic data linkage. Information obtained from the cancer registry included cancer diagnosis coded according to the International Classification of Diseases (ICD) and ICD-O for morphological classification, date and place of cancer diagnosis, and methods used for diagnostic verification. The quality of the BCR data is judged high as measured by the high proportion of microscopically verified cases, 91.5% for men and 94.0% for women for all cancer sites, excluding non-melanoma skin (IARC 2014).

2.5. Ethical considerations

This study was reviewed and approved by the institutional review boards at the Republican Research Center for Radiation Medicine and Human Ecology (Gomel, Belarus) and the National Cancer Institute (Bethesda, MD, USA).

3. Results

3.1. Study cohort

The cohort, established on July 22, 2017, consists of 2,965 subjects with their mothers interviewed for dosimetry/epidemiology questionnaire (Fig. 2) including 26 twins. The cohort represents 94.5% of the 3,138 child-mother pairs who agreed to participate in the study. The remaining 199 mothers (5.5%) could not be interviewed because they were too busy to have personal interview, lived in distant raions, or due to other logistic issues.

At the time of the accident (ATA), most of the mothers (n=2,553, 86.1%) lived in Gomel Oblast while 290 mothers (9.8%) lived in Mogilev Oblast (Fig. 1). For more than 70% of the cohort subjects (2,089), mothers lived in raions most heavily contaminated from the fallout (as shown in filled circles, Fig. 1). Ninety-one mothers (3%) resided outside the study area ATA but had moved into the study area shortly after the accident but before 30 June 1986.

Table 1 presents characteristics of the mothers. At the time of the accident (ATA), mothers were between 15.4 and 45.2 years of age, with a mean of 25.0 and median age of 24.2 years. The large majority (89.3%) were between 18 and 30 years old. At the time of cohort entry (22 July 2017), mothers were between 46.6 and 76.4 years of age (mean of 56.3 y and median of 55.4 y). Slightly less than half were 55 years or younger. At cohort entry, a large majority were either never or former smokers, 87.6% and 3.5%, respectively. Very few mothers reported a personal history of thyroid diseases (3.0%) or treatment with thyroid

hormones before or during pregnancy in 1986 (1.9%). About a quarter of the mothers reported a family history of thyroid disease (N= 749, 25.5%).

Table 2 presents characteristics of the cohort subjects. The cohort was almost equally represented by males and females (50.3% and 49.7%, respectively). Gestational age ATA was distributed almost equally across the pregnancy trimesters: 25.3%, 33.8% and 28.5% for the first, second and third trimester, respectively. For 2.4% of the subjects, conception occurred after the Chernobyl accident. Almost 90% of the cohort had been breastfed during the period between 26 April 1986 and 31 March 1987, and 88.3% of 656 subjects who were born during the period of significant ^{131}I exposure (i.e., between 26 April and 30 June 1986) were breastfed.

More than half of the study subjects (69.4%) were younger than 31 years old at cohort entry. Subjects' mean and median age at cohort entry was 30.8 and 30.9 years, respectively. At cohort entry, most of the study subjects (n=2,409 81.3%) lived in Gomel Oblast, while 282 subjects (9.5%) lived in Mogilev Oblast, 244 subjects (8.2%) lived in Minsk Oblast, and 30 subjects (1.0%) were outside Belarus (Table 2). More than half of the cohort subjects were nonsmokers (57.9%) or former smokers (3.9%); 36.1% were smokers at the time of cohort entry. Fifty-three percent of the cohort subjects reported consuming alcohol less than once a month while almost 20% reported that they had never consumed alcohol.

History of thyroid diseases was reported by 512 subjects (17.3%) – most frequently unspecified diagnoses (n = 204, 6.8%), followed by diffuse goiter (n=121, 4.1%), endemic goiter (n=101, 3.4%), thyroiditis (n=37, 1.2%), hypothyroidism (n=26, 0.9%), Graves' disease (n=8, 0.3%), hyperthyroidism (n=6, 0.2%), thyroid cancer (n=5, 0.2%), and adenoma (n=4, 0.1%).

3.2. Dosimetry

As described in detail in (Drozdovitch *et al* 2019), we estimated radiation doses received by the thyroid from three exposure pathways, internal from ^{131}I intake, external irradiation, and internal from ingestion of cesium isotopes (^{134}Cs and ^{137}Cs); these exposures occurred while *in utero* (prenatal) and/or after birth (postnatal). Predominant exposure to the thyroid occurred during the prenatal period due to ^{131}I intake by mother. The distribution of ^{131}I thyroid doses (pre- and postnatal combined) among the subjects is shown in Table 2. Fifty-four percent of the cohort received ^{131}I dose in the range of 0.01 to 50 mGy. About 6% of the cohort received ^{131}I dose of ≥ 500 mGy, including 55 subjects (1.9%) with the ^{131}I dose of ≥1,000 mGy.

Table 3 compares estimated thyroid doses from the two different exposure pathways and for pre- and postnatal modes of exposure. The mean total (prenatal and postnatal) thyroid dose from the two exposure pathways was 137 mGy, of which prenatal dose (mean, 123 mGy) from ^{131}I intake was the largest contributor. For prenatal exposure, dose from ingestion of ^{134}Cs and ^{137}Cs was minimal (mean, 0.77 mGy), while mean prenatal thyroid dose due to external irradiation was 1.5 mGy. Mean postnatal doses received due to ^{131}I intake, external irradiation and ingestion of radiocaesium isotopes were similar: 6.5 mGy, 3.6 mGy and 1.6 mGy, respectively.

3.3 Thyroid screening

As of August 2019, we had contacted and invited 1,352 cohort subjects for screening examination at the RRCRM&HE. Of these, 1,246 (92.2% of the total) agreed for screening, of whom 867 (69.6%) were examined. Ten persons (0.7%) persons were not examined because of death or serious physical disability, 30 (2.2%) also not examine because of migration, 54 (4.0%) refused because of life events, pregnancy, etc., 12 (0.9%) did not respond.

3.4. Linkage-based cancer ascertainment

We linked the cohort with the BCR to ascertain cancer incident cases. As a result, a total of 29 cases were found, including 5 cases of papillary thyroid cancer, through 31 December 2018. The rest of the cases ascertained by this linkage presented a range of non-thyroid cancers (skin, female genital, urinary system, nervous system), including 10 *in situ* cases, as well as hematological cancers.

4. Discussion

We have constructed a Belarusian cohort of 2,965 persons exposed *in utero* to Chernobyl radioactive fallout. At the time of the accident, most cohort subjects' mothers resided in the most contaminated raions of Gomel and Mogilev oblasts, including the 30-km zone around the Chernobyl nuclear power plant. Individual thyroid doses from combined internal and external sources of irradiation have been reconstructed for all cohort subjects from both prenatal and postnatal (until age of five years) exposure.

This Belarusian cohort was designed to be comparable in population and exposure characteristics to the parallel Ukrainian *in utero* cohort (Table 4). Essentially the same dosimetry model was used to reconstruct thyroid doses for both cohorts. Because a higher proportion of subjects were sampled from heavily contaminated areas, the Belarusian cohort had a higher thyroid dose due to ^{131}I intake than the Ukrainian cohort (mean prenatal dose of 123 mGy for Belarus vs. 73 mGy for Ukraine (Likhtarov *et al* 2011)). In both cohorts, the principal method of follow-up is standardized thyroid screening to ensure systematic ascertainment of cancer and benign conditions of the thyroid. While two cycles of screening have been conducted in the Ukrainian *in utero* cohort, the first cycle of screening is currently in progress in Belarus. In the first year of the 4-year screening cycle, we obtained a participation rate of over 69.6%, which is comparable to that at the recently completed second screening cycle in the Ukrainian *in utero* cohort (Hatch *et al* 2019). In the Belarus cohort, we will continue thyroid screening examinations through 2022. As with the Ukrainian cohort, the Belarusian cohort will also be followed up through the linkage with the BCR to monitor the occurrence of all solid and hematological cancers. The retrospective data from the present linkage-study are difficult to interpret because of potential survival and other selection biases. However, the results do demonstrate the feasibility of future long-term cancer follow-up for this cohort.

An important aspect of our current activities is evaluating uncertainties in questionnaire-based dose estimates due to memory recall. Our previous study (Drozdovitch *et al* 2016)

showed that if dose-related measurements are available for study subjects, the quality of individual behavior and dietary data has, in general, a small influence on the results of the retrospective dose assessment. However, for studies in which dose-related measurements are not available for all study subjects and modeling is used for dose reconstruction, high quality individual behavior and dietary data for the study subjects are required to provide realistic and reliable dose estimates. As the direct thyroid measurements were available only for about 10% of mothers of Belarusian *in utero* cohort members, evaluation of uncertainty in thyroid doses from prenatal and postnatal exposures due to possibly poor memory recall is important for this study. This is the reason why we are conducting a special study to repeat an interview with a sample of 1,200 out of 2,939 mothers using the same study questionnaire that was used during the first interview round in 2012–2017. Information collected from the second round of personal interviews will be used to estimate *de novo* thyroid doses to the study subjects and to compare these estimates with the estimates calculated based on the information from the first interview round. We expect that such approach would allow us to evaluate reliability of questionnaire-based doses due to memory recall in Belarusian *in utero* cohort. So far, we have observed a high participation rate (95.4%) of mothers in the second interview study. The second interview study of the Belarusian *in utero* cohort is in progress and will continue through the beginning of 2022.

Knowledge on the carcinogenic effects of *in utero* exposure to ionizing radiation mainly comes from studies of the atomic bomb survivors in Hiroshima and Nagasaki (Preston *et al* 2008; Delongchamp *et al* 1997) and children born to mothers exposed to diagnostic X-rays during pregnancy (Stewart *et al* 1956; Doll and Wakeford 1997). While these studies have been informative as to the effects of external acute gamma- or diagnostic X-ray irradiation, little is known about effects of protracted exposure or internally incorporated radionuclides. More recently, epidemiological data have become available from populations with accidental or incidental *in utero* exposure, i.e., a cohort of about 8,500 children born to female workers of the Mayak nuclear facility, Russia (Schüz *et al* 2017) and a cohort of about 11,500 individuals exposed *in utero* as a result of their mothers' residence on the radioactively contaminated Techa River territories, Russia (Akleyev *et al* 2016). The Mayak cohort has largely external exposure (Schüz *et al* 2017) while the Techa River cohort has mixed exposure, largely internally from strontium and cesium radioisotopes (Akleyev *et al* 2016). These studies generally have provided data on the radiation-related risk of solid cancers as a group or leukemias but have been much less informative on the risk of specific cancers, especially thyroid cancer, which is a special concern in the case of accidental radioactive releases. In a cross-sectional study of a modest size of atomic bomb survivors exposed *in utero* (n=319), an increased risk, though statistically non-significant, was found for thyroid nodule with an excess odds ratio at 1 Gy of about 2; the small number of thyroid cancer cases (n=5) did not allow dose response analysis (Imaizumi *et al* 2008). As referred to above, in the Ukrainian *in utero* cohort (n=2,582), a significant effect of ^{131}I exposure was found for large thyroid nodules, indictive of a strong radiation effect (a four-fold increase in excess odds ratio); the risk for thyroid cancer was similarly high but not statistically significant, possibly due to the small number of cases (n=8) (Hatch *et al* 2019). Based on the thyroid dose distribution of the cohort, we estimate a study power of 70–96% to detect an excess relative risk per Gy of over 6 for thyroid cancer, assuming that 20 or more thyroid

cancers will have been accrued (Appendix 2). One can reasonably be confident that in the near future this number will be attained by pooling of data from the two Chernobyl *in utero* cohorts.

Health consequences of exposure to radiation *in utero* or in early life are of special concern after accidental radioactive releases from nuclear power plants and other nuclear facilities because of the potential susceptibility of young tissues and the long life of exposed individuals. The Chernobyl accident offers a unique opportunity for learning about the effects of radioiodine exposure. The Belarusian *in utero* cohort described in this paper, together with the parallel Ukrainian cohort, will be a rare opportunity for elucidating thyroid cancer and other health effects of radiation during the gestational period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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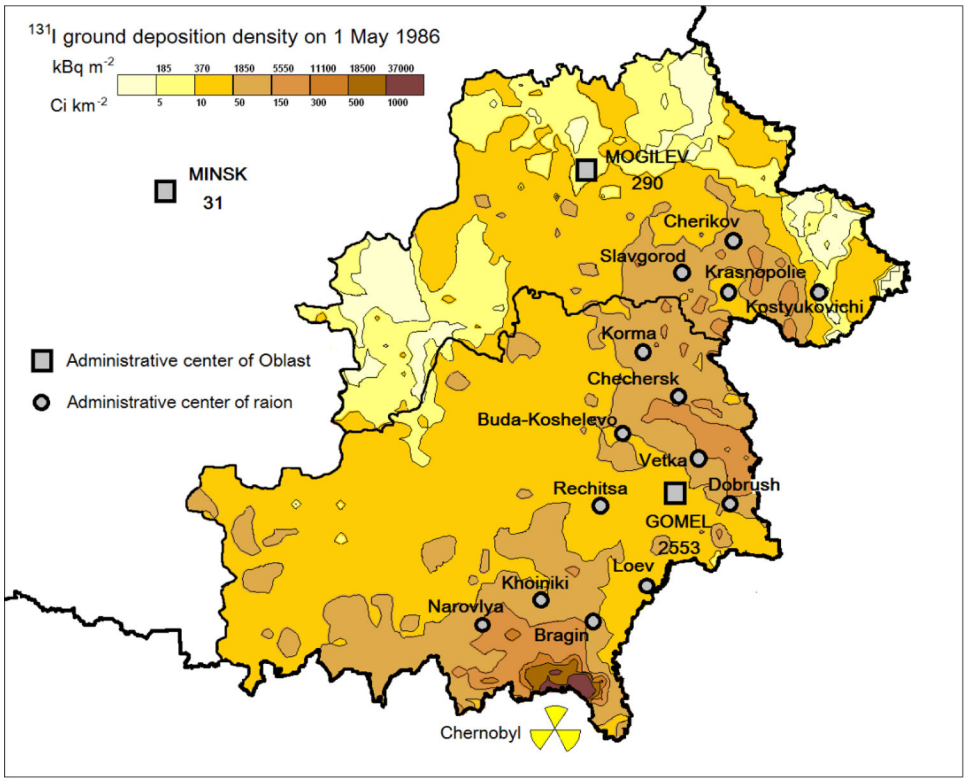

Fig. 1.

Geographical distribution of Belarusian *in utero* cohort members according to their mothers' residence at the time of the Chernobyl accident and ^{131}I ground deposition density on 1 May 1986 in Gomel and Mogilev Oblasts (derived from (Zhukova *et al* 2011)). Administrative center of raions most heavily contaminated from the fallout are shown with filled circles.

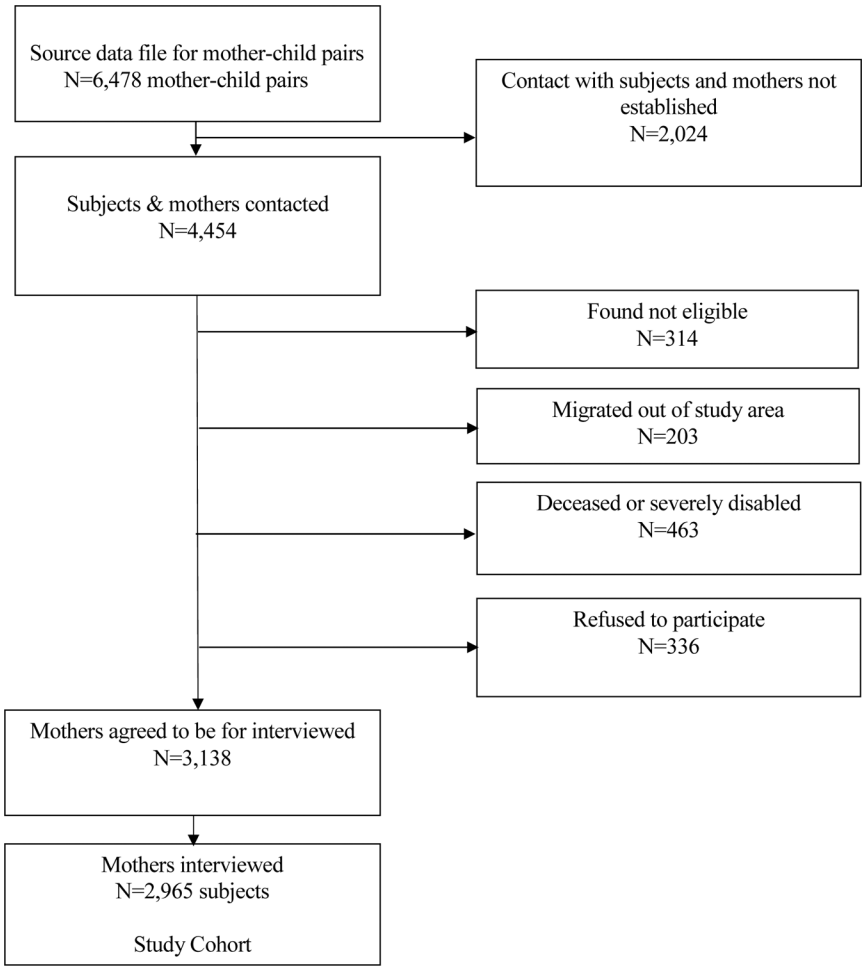

Fig. 2.

Flow chart of Belarusian *in utero* cohort recruitment.

Table 1.

Descriptive characteristics of mothers of the subjects in the Belarusian *in utero* cohort.

Characteristics	Persons	%
Total	2 939[a]	100.0
Age ATA[b] (y)		
<20	401	13.6
20–24.9	1 256	42.7
25–29.9	796	27.1
30–34.9	365	12.5
35–39.9	108	3.7
40+	13	0.4
Oblast of residence ATA		
Gomel	2 553	86.1
Mogilev	290	9.8
Minsk	31	4.1
Age at cohort entry[c] (y)		
<50	146	5.0
50–54.9	1 242	42.2
55–59.9	925	31.5
60–64.9	439	14.9
65+	187	6.4
Smoking status at cohort entry		
Never smoker	2 574	87.6
Former smoker	102	3.5
Smoker	263	8.9
Personal history of thyroid diseases before or during pregnancy in 1986		
No	2 851	97.0
Yes	74	2.5
Unknown	14	0.5
Personal use of thyroid hormones before or during pregnancy in 1986		
No	2 884	98.1
Yes	40	1.4
Unknown	15	0.5
Family history of thyroid diseases		
No	2 135	72.6
Yes	749	25.5
Unknown	55	1.9

[a]Number of mothers is less than the number of study subjects because there were 26 twin births.

[b]ATA is at the time of the accident.

[c]22 July 2017.

Table 2.

Descriptive characteristics of Belarusian *in utero* cohort subjects.

Characteristics	Persons	%
Total	2 965	100.0
Sex		
Male	1 490	50.3
Female	1 475	49.7
Gestation age as of 26 April 1986 (weeks)		
< 0 (conceived after the accident)	368	12.4
0 – 11.9	749	25.3
12 – 25.9	1002	33.8
26 +	846	28.5
Breastfed during 26 April 1986 – 31 March 1987		
No	298	10.1
Yes	2 667	89.9
^{131}I thyroid doses[a] (mGy)		
0	338	11.4
0.01 – 19.9	1 218	41.1
20 – 49.9	392	13.2
50 – 99.9	292	9.8
100 – 199.9	272	9.2
200 – 499.9	290	9.8
500 – 999.9	108	3.6
1000+	55	1.9
Age at cohort entry[b] (y)		
30 – 30.9	2 057	69.4
31 – 31.9	908	30.6
Oblast of residence at cohort entry		
Gomel	2 409	81.3
Mogilev	282	9.5
Minsk	244	8.2
Other	30	1.0
Smoking status at cohort entry		
Never smoker	1 716	57.9
Former smoker	117	3.9
Smoker	1 069	36.1
Unknown	63	2.1
Alcohol consumption at cohort entry		
Never	576	19.4
Once a month or less	1 567	52.8
Several times a month	499	16.8
Once a week	166	5.6

Characteristics	Persons	%
Several times a week	55	1.9
Every day	11	0.4
Unknown	91	3.1
Personal history of thyroid diseases prior to cohort entry		
No	1 692	57.1
Yes	512	17.3
Unknown	761	25.6

[a] Sum of ^{131}I prenatal and postnatal thyroid doses.

[b] 22 July 2017

Table 3.

Thyroid doses in the Belarusian *in utero* cohort from different exposure pathways and modes of exposure (prenatal or postnatal).

Exposure pathway	Thyroid dose, mGy	
	Mean	Median
^{131}I intake, prenatal	123	14
^{131}I intake, postnatal	6.5	0
External irradiation, prenatal	1.5	0.71
External irradiation, postnatal	3.6	2.2
Ingestion radiocesium isotopes, prenatal	0.77	0.53
Ingestion radiocesium isotopes, postnatal	1.6	0.79
All exposure pathways	137	25

Table 4.

Comparison of Belarusian and Ukrainian *in utero* cohorts.

Characteristic	**Belarusian *in utero* cohort**	**Ukrainian *in utero* cohort**
Population size	2 965	2 582
Date of birth	26 April 1986 – 31 March 1987	26 April 1986 – 31 March 1987
Male	1 490	1 229
Female	1 475	1 353
Period of construction	2012 – 2017	2003 – 2006
1st cycle of thyroid screening examination	2018 – 2022	2003 – 2006
2nd cycle of thyroid screening examination	–	2012 – 2015
Number of papillary thyroid cancer cases:		
Prevalent	5	6
Incident	–	2
Mean prenatal thyroid dose due to ^{131}I intake, mGy	123	73