# Title Page

**Risk of thyroid nodules in residents of Belarus exposed to Chernobyl fallout as children and adolescents**

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# Abstract

**PURPOSE:** Several studies have shown an increased risk of thyroid nodules following radiation exposure, but differences in the dose-response for nodules with various characteristics, by age at exposure, iodine deficiency, and other factors are poorly understood.

**METHODS:** We screened 11 970 residents of Belarus aged 18 years or younger at the time of the Chernobyl nuclear accident for thyroid disease. Screening consisted of thyroid palpation, ultrasonography, and medical follow-up when appropriate. Demographic information and medical history were collected using standardized questionnaires. All 11 421 eligible participants had thyroid glands at screening and estimated I-131 thyroid doses based on individual thyroid activity measurements.

**RESULTS:** Radiation dose was related to higher odds of any thyroid nodule (N cases=881) in the entire dose range (0 to 39 gray). For doses between 0 and 5 gray, a linear dose-response model revealed excess odds ratios (95% confidence intervals) of 0.70 (0.33, 1.18) for all nodules, 0.33 (<0.04, 0.70) for non-neoplastic nodules, 3.83 (0.89, 15.45) for neoplastic nodules, 0.27 (<0.07, 0.71) for nodules less than 10 mm in diameter, 2.13 (0.97, 4.59) for nodules 10 mm or greater, 0.67 (0.30, 1.19) for single nodules, and 0.61 (<0.23, 2.03) for multiple nodules centered for a participant aged 5 at the time of the accident. Risk associated with radiation dose increased significantly with younger age at the time of the accident for all nodules combined and all major nodule groupings.

**CONCLUSION:** The current study expands some previous findings of radiation-related risks of thyroid nodules to young adults and provides new evidence for dose-response relationships by histological and ultrasound characteristics.

# **Manuscript**

## Introduction

Thyroid nodules are a common ultrasonographic (US) finding, usually with few direct clinical implications. However, nodules larger than 10 mm in diameter or having other suspicious features may require further evaluation to rule out diagnosis of thyroid cancer[1](#_ENREF_1). While only 5 to 15% of nodules are found to be malignant[1-4](#_ENREF_1), malignancy rates of over 30% have been reported among patients with a history of therapeutic radiation[5](#_ENREF_5)[6](#_ENREF_6) and ionizing radiation is one of the most established risk factors for thyroid cancer[1](#_ENREF_1).

Despite the thyroid’s sensitivity to radiation-induced carcinogenesis, only a few epidemiological studies have evaluated the relationship between radiation dose and risk of screen-detected thyroid nodules[7-12](#_ENREF_7). These studies have either reported an increased radiation-related risk for any thyroid nodule[8-10](#_ENREF_8)[12](#_ENREF_12) or no association[7](#_ENREF_7)[11](#_ENREF_11). Fewer studies have evaluated the radiation-dose response by nodule behavior[7-9](#_ENREF_7)[12](#_ENREF_12) and only one has examined the radiation dose-response by nodule size[12](#_ENREF_12). In a sample of 2 668 Japanese atomic bomb survivors 62 years and older, Imaizumi and colleagues reported a significant increasing dose-response relationship for all, malignant, and benign nodules with diameter ≥ 10 mm, but no significant dose-response relationship for nodules < 10 mm[12](#_ENREF_12). Radiation dose-response relationships for thyroid nodules have not been reported in a screened population of young adults who may have a smaller proportion of thyroid nodules and a shorter time since radiation exposure. Differences in the radiation dose-response relationships for single *versus* multiple nodules have also not been examined, although malignancy risk among patients presenting with single *versus* multiple nodules continues to be of interest to the clinical community[4](#_ENREF_4)[13](#_ENREF_13)[14](#_ENREF_14).

The objective of this study is to assess the relationship between radiation exposure and prevalent thyroid nodules diagnosed during the first screening cycle in Belarus. This is a population-based study of 11 970 participants who were exposed as children and adolescents to radioactive I-131 from fallout as a result of the Chernobyl Nuclear Power Plant accident. To our knowledge, this is the largest study of thyroid radiation exposure in relation to screen-detected thyroid nodules and the first to directly compare the radiation dose-response for nodules of varying histological/cytological and US features in young adults.

## Materials and Methods

### Study Population

Detailed descriptions of the cohort and methods have been previously described[15-17](#_ENREF_15). Briefly, 11 970 individuals residing in Belarus who were aged 18 years or younger at the time of the Chernobyl accident (26 April 1986) with thyroid radioactivity measurements were screened for thyroid diseases (11 903 from 1996-2001 and 67 from 2002-2004). We excluded (in series) participants outside the age range of 0 to 18 years (inclusive) at the time of the accident (n=114), those with unknown doses (n=124), unknown or zero thyroid volume (n=165), self-reported history of thyroid cancer (n=2), aplasia (n=4), thyroid surgery (n=21), and those who reported past or current use of thyroid hormones as part of their medical history (n=119). Our final study population included 11 421 subjects at risk of prevalent thyroid nodules at the time of screening.

### Screening Protocol

Study subjects were screened for thyroid disease at medical centers in Minsk and Gomel cities or at local medical clinics by visiting mobile screening teams. Screening consisted of thyroid palpation and US examination by a trained sonographer, and a clinical examination with independent palpation by an endocrinologist. Any discrepancies were resolved by a third examination conducted jointly by both professionals. Participants were also administered standardized questionnaires to ascertain demographic information, location of residence, dietary and medical history. Blood and spot urine samples were collected to measure thyroid hormone levels and urinary iodine concentration, respectively. This study was approved by institutional review boards in Belarus and the United States. Informed consent was provided by the study participants or accompanying guardians for minors.

### Ascertainment and Classification of Thyroid Nodules

Prevalent thyroid nodules were ascertained from thyroid US (Machine XX) by certified US technologists to detect nodules with maximum diameter of 3 mm or larger. Participants with solid nodules that were 1) 10 mm or larger in diameter or 2) 5 to 9 mm with suspicious US features (hypoechogenic, indistinct border, calcified inclusions, extension through the thyroid capsule or suspicious lymphadenopathy) or with diffusely abnormal thyroid tissue accompanied by unexplained cervical lymphadenopathy were referred to the Minsk and Gomel study centers for further evaluation and US-guided fine needle biopsy (FNB). All medical personnel were blinded to radiation doses.

Participants were classified as cases if they had at least one US-detected nodule. We classified cases into individuals with neoplastic, suspicious, and non-neoplastic nodules. Neoplastic cases include people with thyroid cancer and/or follicular adenoma detected during the first screening and histologically confirmed through surgery. Suspicious nodules included those people who were referred to FNB and/or surgery, but did not comply and people with a cytological result of inadequate, indeterminate, suspicious, or neoplastic who never underwent surgery for histological confirmation. Non-neoplastic nodule cases included people without suspicious features that were not referred to FNB or surgery (including people who had been evaluated prior to this screening) and cases that were confirmed to be non-neoplastic either through FNB and/or surgery. We also categorized participants with single *versus* multiple nodules and small (< 10 mm) *versus* large nodules (≥ 10 mm). Among participants with multiple nodules, nodule size was represented by the nodule with the largest maximum diameter. Similarly, among people with multiple nodules, the most serious cytological finding or highest level of intervention was chosen. For example, if a person was referred to FNB for one nodule, but not another, they were considered to be “referred to FNB”.

### Thyroid Radiation Dose

Radiation exposure to the thyroid gland came primarily from intake of I-131 through air inhalation, consumption of contaminated milk, dairy products, and leafy vegetables[18](#_ENREF_18). Thyroid dose estimation for each cohort member was based on I-131 activity in the thyroid derived from direct thyroid measurements, a radio-ecological model used to assess the temporal variation of I-131 in the thyroid, and personal interviews, which provided information on individual dietary and lifestyle habits. The results of direct thyroid measurements in Belarus were corrected for contribution to the measured signal from external surface contamination of body and clothes as well as internal contamination of cohort member's body with cesium isotopes. The following data sources were used to update the parameters of the dosimetry model, including thyroid volume measurements from the Sasakawa Memorial Foundation to derive age-specific thyroid masses[19](#_ENREF_19); measurements of I-131 in soil to verify the validity of calculated I-131 deposition density in each settlement; and I-131 measurements in soil and grass samples to derive an interception factor of I-131 by vegetation[20](#_ENREF_20). The arithmetic mean of 1,000 individual stochastic doses due to I-131 intake, which were calculated for each cohort member, was used to characterize thyroid radiation dose[21](#_ENREF_21).

### Statistical Analysis

To evaluate the relationship between thyroid radiation dose and prevalent thyroid nodules, we fit a linear excess odds ratio (EOR) model of the following form:

where is the baseline log-linear odds of thyroid nodules as a function of a vector of confounding factors *x* at 0 Gy, d is radiation dose, and *z* is a vector of covariates representing effect modification variables. Parameters α, β, and γ are estimated by the model. To test for presence of non-linearity we also considered the following linear-quadratic model:

and a linear-exponential model of the form:

and tested whether parameter δ=0 for both linear-quadratic and linear-exponential models.

The following variables were considered potential confounders because they could be significantly associated with both radiation dose and thyroid nodules, but not believed to be on the causal pathway: sex, age at screening, smoking history (ever/never), oblast of residence (Gomel, Minsk, Others), urban status (urban/rural residence), self-reported family history of thyroid disease, and measures of iodine deficiency including urinary iodine concentration, thyroid enlargement (thyroid volume >18 ml for women and >25 ml for men), and presence of diffuse goiter upon palpation at screening. These factors, age at the time of the accident, and age at time of the accident with a spline at age 5 were tested as potential effect modifiers of the radiation dose-response. Missing values were coded as separate categories and included as indicator variables in the models. Potential confounders that significantly improved the model fit for odds of any thyroid nodule were included in the background risk (at zero radiation dose) for continuous dose-response models. To enable meaningful comparisons across different types of nodules with smaller sample sizes (e.g. non-neoplastic large nodules), some results are presented using more parsimonious background models chosen by excluding factors with the least impact on risk estimates. P-values were computed based on likelihood ratio tests comparing nested models. The Akaike information criterion (AIC) was chosen to compare non-nested models (e.g. linear-quadratic *versus* linear-exponential models). All statistical tests were two-sided with a specified type I error of 0.05, and 95% confidence intervals (CIs) were estimated with maximum likelihood procedures. Model fitting was carried out using the GMBO module of the software package Epicure (Hiro Soft Int. Corp.)[22](#_ENREF_22).

## Results

### Characteristics of screen-detected thyroid nodules

Thyroid nodules were detected at screening among 8% (n cases=881) of 11 421 eligible participants (**Table 1**). Among persons with at least one thyroid nodule, 11% (n=101) were diagnosed with a neoplasm (66 with thyroid cancer only, 24 with follicular adenoma only, and 11 with both). A neoplasm was diagnosed in a greater proportion of people with large nodules than small nodules and people with single *versus* multiple nodules detected through US.

### Background risk factors for all thyroid nodules

Nodule prevalence was higher in participants older at screening, females *versus* males (OR=1.50; 95% CI: 1.31, 1.73), participants with thyroid enlargement (OR=2.83; 95% CI: 2.29, 3.48), diffuse goiter detected at screening (OR=3.26; 95% CI: 2.80, 3.81), and family history of thyroid disease (OR=1.85; 95% CI: 1.49, 2.27), but lower among persons with adequate urinary iodine concentration (≥ 100 μg/l) compare to insufficient (< 20 μg/l) urinary iodine at screening (OR=0.78; 95% CI: 0.62, 0.98) (**Table 2**). Urban status and oblast of residence at screening did not significantly affect the prevalence of thyroid nodules. Thyroid radiation doses ranged from nearly 0 to 39 Gy, with 80% of participants exposed to < 5 Gy.

### Radiation-related risk of thyroid nodules

The prevalence of all nodules, non-neoplastic, neoplastic, small, large, single, and multiple nodules was significantly associated with thyroid radiation dose across the full dose range (P for trend < 0.001 for all nodule types, **Table 3**). Over the entire dose range of 0 to 39 Gy, the dose-response pattern was linear for all nodules combined and for most nodule groupings; however, for non-neoplastic and multiple nodule types linear-exponential dose-response models provided improved fits to the data than simple linear models (**Table S1**).

In the 0 to 5 Gy dose range, the shapes of the dose-response patterns were linear for all nodule groupings with estimated EORs of 0.70 (0.33, 1.18) for all nodules, 0.33 (<0.04, 0.70) for non-neoplastic, 3.83 (0.89, 15.45) for neoplastic, 0.27 (<0.07, 0.71) for small (< 10 mm), 2.13 (0.97, 4.59) for large (≥ 10 mm), 0.67 (0.30, 1.19) for single, and 0.61 (<0.23, 2.03) for multiple nodules centered for a person aged 5 at the time of the accident (**Figure 1**). Further analyses are restricted to the 0 to 5 Gy dose range.

### Effect modification of radiation dose-response

Age at the time of the accident significantly modified the dose-response relationships for major nodule groupings so that earlier age at the time of the accident was associated with a higher EOR per Gy compared with older children and adolescents (**Figure 2, Table 4, Table S1**). In the 0 to 5 Gy dose range, for each 1-year increase in age at the time of accident, the EORs per Gy changed by a factor of 0.79 (0.68, 0.87) for all nodules, 0.83 (0.25, 0.96) for non-neoplastic, 0.75 (0.60, 0.90) for neoplastic, 0.73 (0.25, 0.90) for small (< 10 mm), 0.79 (0.70, 0.89) for large (≥ 10 mm), 0.82 (0.70, 0.90) for single, and 0.68 (0.20, 0.88) for multiple nodules.

We also observed a significant interaction for sex (P = 0.005) in the dose-response relationship of multiple nodules so that the EORs were 0.10 (< 0.61, 3.60) in men and 1.40 (<-0.22, 3.59) in women **(Table S1).**  We did not detect a significant interaction with urban status, oblast of residence, urinary iodine concentration, enlarged thyroid volume, diffuse goiter, or family history of thyroid disease for any of the major nodule groupings (**Table S2).**

### Differences in radiation-related risk by thyroid nodule groupings

We further examined potential differences in the radiation dose-response by various nodule types in **Figure 3**. EORs were centered for a person aged 2 at the time of the accident and restricted to the linear dose range of 0 to 5 Gy. The radiation dose-response was higher for neoplastic *versus* non-neoplastic nodules (P = 0.002) and large *versus* small nodules (P = 0.003). Among non-neoplastic nodules, a higher dose-response was observed for large compared to small nodules (P = 0.044). Among neoplastic nodules, there was no difference in the dose-response relationship between large and small nodules (P > 0.5). Among small nodules, a non-significantly higher dose-response was observed for neoplastic nodules compared to non-neoplastic nodules (P = 0.084). Similarly, among large nodules, a non-significantly higher dose-response was observed for neoplastic nodules compared to non-neoplastic nodules (P = 0.242). No significant difference was detected in the dose-response for single *versus* multiple nodules overall, or within sex strata (data not shown).

## Discussion

This is the largest population-based study of radiation exposure in relation to thyroid nodules and the first study in a screened population of young adults. We found I-131 thyroid dose to be significantly associated with increased risk of all thyroid nodules combined and the mutually exclusive categories of non-neoplastic/suspicious/neoplastic, single/multiple, and small (< 10 mm)/large (≥ 10 mm). The dose-response relationships for these classifications of nodules were modified by age at time of the accident so that risk increased with younger age at exposure.

Our findings support previous research demonstrating an increased radiation-related risk of thyroid nodules[23-25](#_ENREF_23). Focusing main analyses to nodules ≥10 mm, Imaizumi and colleagues found significantly increased risk of all nodules (EOR=1.65), benign nodules (EOR=2.07), malignant tumors (EOR=4.40), and nodules not otherwise specified (EOR=0.68) for a person aged 5 at exposure to external gamma radiation[12](#_ENREF_12). Our population was primarily exposed to internal I-131 and our nodule groupings are also not completely consistent. For example, we combine malignant thyroid cancer with follicular adenoma into a ‘neoplastic’ group because both outcomes have shown similar increasing radiation-related risks in this cohort[16](#_ENREF_16)[26](#_ENREF_26) and our ‘non-neoplastic’ grouping includes nodules that were not referred for FNB or surgery. Despite these differences, for nodules ≥ 10 mm, we found similar significantly increased risks for all (EOR=2.13), non-neoplastic (EOR=1.63), and neoplastic nodules (EOR=4.20) in the 0 to 5 Gy dose-range for a person aged 5 at exposure (**Table S1**). Our suspicious grouping is similar to that study’s “not otherwise specified” group in that it includes cases with inadequate or indeterminate cytological finds; however, it is not restricted to large nodules and also includes cases with suspicious US findings that did not receive the recommended diagnostic follow-up. For suspicious nodules, we found a significant increased risk as well.

We formally evaluated differences in the radiation-related dose-response for neoplastic *versus* non-neoplastic thyroid nodules for age 2 at the time of the accident (**Figure 3**), finding a statistically higher dose-response relationship for neoplastic nodules (P = 0.002). The dose-response was also higher for neoplastic nodules within small and large nodule subsets, though differences did not achieve statistical significance. Under the traditional paradigm of radiation exposure causing a series of somatic mutations leading to neoplasm, these findings suggest that radiation-induced somatic mutations may play a smaller role in the occurrence of non-neoplastic nodules. Due to the cross-sectional design of this study, we do not know whether non-neoplastic nodules became neoplastic from radiation exposure or whether the behaviors of these nodules were apparent from their onset. Prospective follow-up of the cohort will be informative in this regard.

In contrast to findings by Imaizumi and colleagues, we did observe a small, but significant radiation-related risk of small nodules (< 10 mm in diameter). A partial explanation for this difference may rest in the much younger age distribution of our study population. In our study of 10 to 34 year olds, small nodules were far less common (881/11421 = 5%) than among the 62 to 75-year-old Japanese atomic bomb survivors (667/3087 = 22%). Because the prevalence of thyroid nodules increases with age[27](#_ENREF_27), the radiation dose-response in atomic bomb survivors may have been attenuated by a larger proportion of sporadic small nodules that occurred during the 62 to 66 years between radiation exposure and screening. To our knowledge this is only the second study to evaluate the dose-response for small nodules and apparent inconsistencies between studies warrant further investigation.

We also evaluated differences in the radiation-related dose-response for small *versus* large thyroid nodules (centered for children aged 2 at the time of the accident), finding a statistically higher dose-response relationship for large nodules (P = 0.003) and for large nodules among non-neoplastic nodules (P = 0.044), but not among neoplastic nodules (P > 0.5). The overall differences may be partially explained by the larger proportion of large nodules that were also neoplastic compared to small nodules (**Table 1**). However, the findings of a stronger dose-response for large nodules non-neoplastic *versus* small non-neoplasticnodules suggest that either the etiology of small and large nodules varies with regard to radiation exposure or that radiation may play an important role in nodule growth. In a longitudinal study of benign thyroid nodules, Durante and colleagues reported nodule growth in only 15% of patients over a period of 5 years[28](#_ENREF_28). Prospective follow-up of this cohort may provide important evidence for the role of radiation exposure on nodule size.

To our knowledge this is the first study to evaluated differences in the radiation dose-response relationship for single *versus* multiple nodules. Our data suggest that radiation exposure plays a similar role for both US findings. However, for multiple nodules, we found a significant interaction by sex so that a significant dose-response was only observed among women. Other demographic, iodine deficiency-related, and genetic factors did not significantly modify the dose-response relationship although it tended to be stronger for participants with iodine deficiency as indicated by urinary iodine concentration, enlarged thyroid volume, and diffuse goiter (**Table S2**).

Our findings of increased risk of thyroid nodules associated with radiation exposure at a young age are consistent with previous findings for thyroid nodules[9](#_ENREF_9)[12](#_ENREF_12)[26](#_ENREF_26)[29](#_ENREF_29) and for thyroid cancer and follicular adenoma in this cohort[16](#_ENREF_16)[26](#_ENREF_26). These results support the hypothesis that early childhood constitutes a window of increased susceptibility to the effects of radiation. Although based on limited human data, this view attributes increased cancer susceptibility in early childhood to more frequent cell division with inadequate time for DNA repair of mutations and an immune system that is not yet fully developed[30](#_ENREF_30).

In summary, in this large population-based screening study, exposure to I-131 was significantly associated with increased risk of thyroid nodules. The relationship of I-131 and thyroid nodules was particularly evident in participants who were under the age of 5 at exposure. Future studies should focus on progression of prevalent thyroid nodules and incidence of thyroid nodules during subsequent screening cycles.

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# Tables and Figures

## Table 1. Histological and cytological results of thyroid nodules by US findings of size and singularity.

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| |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | |  |  |  | **Size** | |  | | **Singularity** | | | | **Histological or cytological diagnosis** | **Total** |  | **Small (< 10 mm)** | **Large (≥ 10 mm)** | |  | | **Single** | **Multiple** | | | All nodules | 881 |  | 602 | 279 | |  | | 648 | 233 | | | Non-neoplastic nodules | 576 |  | 463 | 113 | |  | | 414 | 162 | | | Not referred for FNB or surgery1 | 450 |  | 412 | 38 | |  | | 322 | 128 | | | Confirmed non-neoplastic2 | 126 |  | 51 | 75 | |  | | 92 | 34 | | | Suspicious nodules3 | 204 |  | 111 | 93 | |  | | 155 | 49 | | | Neoplastic nodules4 | 101 |  | 28 | 73 | |  | | 79 | 22 | | | Thyroid cancer only | 66 |  | 19 | 47 | |  | | 52 | 14 | | | Follicular adenoma only | 24 |  | 6 | 18 | |  | | 21 | 3 | | | Thyroid cancer and follicular adenoma5 | 11 |  | 3 | 8 | |  | | 6 | 5 | | |

Abbreviations: US, ultrasound; FNB, fine needle biopsy.

1 Includes cases with pre-screened non-neoplastic thyroid nodules and cases of diffuse goiter. For large non-neoplastic nodules, this includes 2 people with nodules initially measured < 10 mm, 23 people with pre-screened thyroid nodules and 13 people with diffuse goiter.

2 Referred to FNB and/or surgery, FNB and/or surgery completed with confirmation of no neoplasm.

3 FNB and/or surgery recommended, but refused (includes 6 cases who were suspected and went on to be diagnosed through surgery with a neoplasm >3 years from ultrasound).

4 Neoplastic prevalent cases.

5 Incidental findings during surgery for 6 cases of both thyroid cancer and follicular adenoma, although only single nodule ascertained by ultrasound.

## Table 2. Characteristics of 11 421 residents of Belarus exposed to Chernobyl fallout.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | |  | **Cases2** | | **Non-cases** | |  | | **Characteristic 1** | **N** | **Percent** | **N** | **Percent** | **OR (95% CI)3** | | Sex |  |  |  |  |  | | Male | 348 | 40 | 5232 | 50 | Ref. | | Female | 533 | 60 | 5308 | 50 | 1.50 (1.31, 1.73) | | Age at screening, years | |  |  |  |  | | 10 to 17 | 168 | 19 | 3343 | 32 | Ref. | | 18 to 24 | 329 | 37 | 4178 | 40 | 1.57 (1.30, 1.90) | | 25 to 34 | 384 | 44 | 3019 | 29 | 2.53 (2.10, 3.06) | | Oblast of residence at screening | | | | | | | Minsk | 208 | 24 | 2922 | 28 | Ref. | | Gomel | 587 | 67 | 6440 | 61 | 1.15 (0.97, 1.36) | | Other | 86 | 10 | 1178 | 11 | 0.90 (0.69, 1.16) | | Urban status at screening | | | | | | | Rural | 333 | 38 | 4172 | 40 | Ref. | | Urban | 548 | 62 | 6368 | 60 | 1.08 (0.94, 1.25) | | Urinary iodine concentration, μg l-1 | | | | | | | 0 to 19 | 115 | 13 | 1147 | 11 | Ref. | | 20 to 99 | 470 | 53 | 5710 | 54 | 0.81 (0.65, 1.01) | | 100 to 2120 | 288 | 33 | 3545 | 34 | 0.78 (0.62, 0.98) | | Unknown | 8 | 1 | 138 | 1 | 0.56 (0.25, 1.10) | | Thyroid enlargement4 | |  |  |  |  | | No | 752 | 85 | 10034 | 95 | Ref. | | Yes | 129 | 15 | 506 | 5 | 2.83 (2.29, 3.48) | | Diffuse goiter detected during screening | | | | | | | No | 590 | 67 | 8940 | 85 | Ref. | | Yes | 290 | 33 | 1575 | 15 | 3.26 (2.80, 3.81) | | Unknown | 1 |  | 25 | 0 | 0.61 (0.03, 2.94) | | Any family history of thyroid disease | | | | | | | No | 743 | 84 | 9513 | 90 | Ref. | | Yes | 116 | 13 | 863 | 8 | 1.85 (1.49, 2.27) | | Unknown | 22 | 2 | 164 | 2 | 1.68 (1.04, 2.59) | | Thyroid radiation dose, Gy | | |  |  |  | | 0 to 0.09 | 231 | 26 | 2972 | 28 | Ref. | | 0.10 to 0.24 | 169 | 19 | 2138 | 20 | 1.03 (0.84, 1.27) | | 0.25 to 0.49 | 158 | 18 | 1961 | 19 | 1.06 (0.86, 1.31) | | 0.50 to 0.99 | 129 | 15 | 1682 | 16 | 1.08 (0.86, 1.35) | | 1.00 to 1.99 | 110 | 12 | 1076 | 10 | 1.54 (1.21, 1.95) | | 2.00 to 4.99 | 55 | 6 | 565 | 5 | 1.65 (1.20, 2.24) | | 5.00 to 38.90 | 29 | 3 | 146 | 1 | 4.39 (2.79, 6.69) | |

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; Ref., reference; Gy, gray.

1 Person with any nodule identified through ultrasound at first screening.

2 Participants excluded if age at time of accident <0 or >18, missing dose, history of thyroid cancer, thyroid surgery, no thyroid, or history of thyroid hormone intake.

3 All factors adjusted for log age at screening except age at screening.

4 Thyroid enlargement defined as thyroid volume >18 ml for women and >25 ml for men.

## Table 3. Odds ratios and 95% confidence intervals for thyroid nodules across thyroid radiation dose categories among 11 421 residents of Belarus exposed to Chernobyl fallout.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | |  | **Thyroid radiation dose (Gy)** | | | | | | | **Type of nodule\*** | **0.10 to 0.24** | **0.25 to 0.49** | **0.50 to 0.99** | **1.00 to 1.99** | **2.00 to 4.99** | **5.00 to 38.90** | | All nodules | 1.11 (0.84, 1.59) | 1.36 (1.02, 1.91) | 1.44 (1.06, 2.06) | 2.40 (1.59, 3.55) | 2.38 (1.56, 3.67) | 5.14 (2.88, 8.79) | | *Behavior* |  |  |  |  |  |  | | Non-neoplastic | 0.93 (0.67, 1.39) | 1.16 (0.83, 1.64) | 1.09 (0.74, 1.64) | 1.77 (< 0.71, 2.83) | 1.45 (0.95, 2.38) | 3.85 (< -0.88, 7.32) | | Suspicious | 2.53 (1.09, 6.20) | 3.47 (1.34, 8.55) | 3.15 (1.28, 8.07) | 5.32 (2.32, 12.9) | 6.51 (2.40, 18.9) | 15.3 (4.91, 45.8) | | Neoplastic | 1.29 (< -0.98, 5.84) | 1.79 (< 0.43, 6.41) | 3.01 (< 0.01, 10.2) | 5.14 (< -0.90, 18.2) | 6.57 (1.75, 26.1) | 8.13 (< 0.12, 36.1) | | *Size* |  |  |  |  |  |  | | <10 mm | 1.11 (0.80, 1.70) | 1.18 (0.87, 1.73) | 1.46 (1.02, 2.23) | 1.93 (1.19, 3.04) | 1.49 (0.99, 2.47) | 3.88 (1.66, 7.50) | | ≥10 mm | 1.22 (0.70, 2.45) | 2.26 (1.23, 4.36) | 1.57 (0.86, 3.12) | 4.65 (2.47, 8.95) | 6.38 (3.13, 13.0) | 11.0 (4.83, 24.7) | | *Singularity* |  |  |  |  |  |  | | Single | 1.24 (0.87, 1.86) | 1.33 (0.95, 1.96) | 1.52 (1.05, 2.30) | 2.45 (1.57, 3.76) | 2.41 (1.51, 3.90) | 4.99 (2.68, 8.97) | | Multiple | 0.84 (< 0.45, 1.38) | 1.42 (< 1.21, 2.80) | 1.26 (< 0.72, 2.44) | 2.21 (< -1.15, 4.91) | 2.21 (< 0.09, 5.26) | 5.44 (< -2.60, 15.3) | |

Abbreviation: Gy, gray.

\* All models use reference group of 0 to 0.09 Gy and adjust for sex, log age at screening, urban status at screening, oblast of residence at screening (Minsk, Gomel, Other), enlarged thyroid volume (defined as thyroid volume >18 ml for women and >25 ml for men), diffuse goiter detected during screening, any family history of thyroid disease and centered for participants aged 5 at time of the accident. P < 0.001 for test of linear trend with dose categories coded 1 thru 7 for all nodule groupings.

## Table 4. Radiation-related excess odds ratios (EORs) and 95% confidence intervals (CIs) for thyroid nodules by age at time of the Chernobyl accident in Belarus.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  | | --- | --- | --- | --- | |  | **EOR/Gy (95% CI) by age at time of accident**†**, years** | | | | **Type of nodule** | **0 to 1.9** | **2.0 to 4.9** | **5.0 to 18.9** | | All nodules | 1.28 (0.64, 2.24) | 0.67 (0.24, 1.29) | 0.18 (0.03, 0.37) | | *Nodule behavior* |  |  |  | | Non-neoplastic | 0.52 (0.07, 1.30) | 0.21 (-0.11, 0.75) | 0.10 (-0.05, 0.32) | | Suspicious | 2.45 (0.68, 6.46) | 0.93 (0.05, 2.84) | 0.30 (-0.01, 0.81) | | Neoplastic | 7.17 (2.02, 24.24) | 5.83 (1.74, 17.1) | 0.84 (0.13, 2.52) | | *Nodule size* |  |  |  | | Small (<10 mm) | 0.77 (0.22, 1.68) | 0.36 (-0.03, 0.98) | 0.05 (-0.09, 0.25) | | Large (≥10 mm) | 2.76 (1.09, 6.12) | 1.52 (0.49, 3.45) | 0.54 (0.19, 1.09) | | *Singularity* |  |  |  | | Single | 1.00 (0.41, 1.95) | 0.64 (0.19, 1.34) | 0.20 (0.03, 0.43) | | Multiple, all | 2.56 (0.76, 2.33) | 0.70 (-0.07, 2.33) | 0.15 (-0.07, 0.53) | | Multiple, Men | -0.37 (-1.59, 2.23) | 0.46 (< -1.71, 2.64) | -0.05 (< -0.35, 0.36) | | Multiple, Women | 4.75 (1.39, 13.77) | 0.86 (-0.26, 3.70) | 0.36 (-0.03, 1.10) | |

\* Models adjusted for sex, log age at screening, urban status at screening, oblast of residence at screening (Minsk, Gomel, Other), thyroid enlargement, goiter detected at screening, and self-reported family history of thyroid disease. Restricted to participants exposed to less than 5 Gy.

† Means of age categories: 0 to 1.9, 1.1 years; 2.0 to 4.9, 3.5 years; 5.0 to 18.9, 10.9 years.

## Figure 1. Radiation-related odds ratios\* and 95% confidence intervals for thyroid nodules in Belarus.



\* All models adjusted for sex, log age at screening, urban status at screening, oblast of residence at screening (Minsk, Gomel, Other), thyroid enlargement, goiter detected at screening, self-reported family history of thyroid disease and are centered for a person aged 5 years old at time of the accident. Restricted to participants exposed to less than 5 Gy.

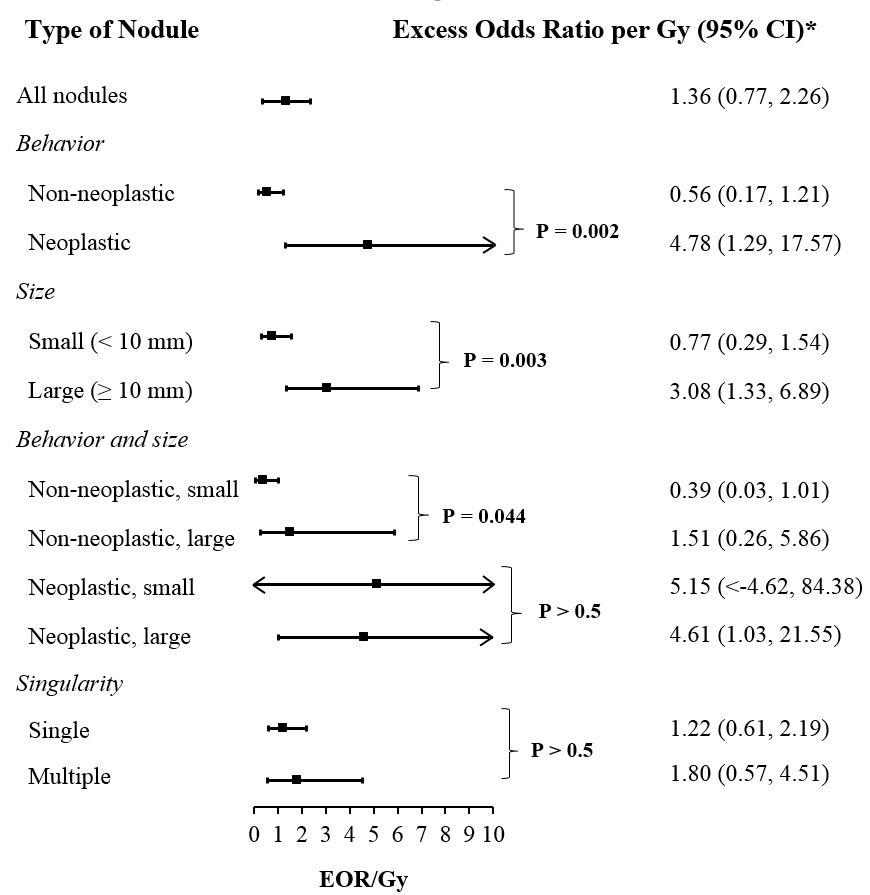
† Sex-specific EORs for multiple nodules are 0.10 (<0.61, 3.60) in men and 1.40 (<-0.22, 3.59) in women.

## Figure 2. Radiation-related odds ratios\* and 95% confidence intervals for thyroid nodules by age at time of Chernobyl accident in Belarus.



\* All models adjusted for sex, log age at screening, urban status at screening, oblast of residence at screening (Minsk, Gomel, Other), thyroid enlargement, goiter detected at screening, and self-reported family history of thyroid disease. Non-parametric point estimates use tertile cutoffs of 5 and 10 years old. Restricted to participants exposed to less than 5 Gy.

## Figure 3. Radiation-related excess odds ratios and 95% confidence intervals for thyroid nodules in Belarus.



\* Adjusted for sex, log age at screening, urban/rural residence at screening and centered at age 2 years old at the time of the accident. P-values for differences in dose-response relationships between nodule groupings based on likelihood ratio tests. Among small nodules, difference between non-neoplastic and neoplastic P = 0.084. Among large nodules, difference between non-neoplastic and neoplastic P = 0.242. Restricted to participants exposed to less than 5 Gy.

## Table S1. Radiation dose-response for the prevalence of thyroid nodules in Belarus, 0 to 39 Gy and 0 to 5 Gy.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | | **Dose range: 0 to 39 Gy** | | | | | | | | |  |  | **EOR (95% CI)/Gy, βdose\*exp(δdose)1** | | **P-values2** | | | | |  | **N** |  | **Linear term, β;** | **Age at** |  | **Lin-** | **Lin-** | | **Type of nodule** | **cases** | **Model** | **Linear-exponential term, δ** | **accident** | **Sex** | **exp** | **quad** | | All nodules | 881 | Linear | 0.59 (0.30, 0.98) | <0.001 | >0.5 | 0.29 | 0.41 | | *Nodule behavior* |  |  |  |  |  |  |  | | Non-neoplastic, all | 576 | Linear | 0.36 (0.07, 0.68) | <0.001 | 0.104 | 0.008 | 0.034 | |  |  | Lin-exp\* | 0.15 (<-0.07, 0.41); 0.09 (0.02, 0.21) |  |  |  |  | | Not referred for FNB/surgery | 450 | Linear | 0.18 (0.01, 0.42) | 0.04 | 0.06 | >0.5 | >0.5 | | Confirmed non-neoplastic | 126 | Linear | 1.89 (<-0.30, 5.84) | 0.001 | >0.5 | 0.196 | 0.319 | | Suspicious | 204 | Linear, all | 1.25 (0.35, 3.36) | <0.001 | 0.02 | >0.5 | >0.5 | |  |  | Linear,  sex-specific\* | 2.38 (0.73, 6.56) among men 0.65 (0.14, 2.12) among women |  |  |  |  | | Neoplastic | 101 | Linear | 2.12 (0.37, 8.37) | 0.004 | 0.356 | 0.225 | NE | | *Nodule size* |  |  |  |  |  |  |  | | Small (<10 mm) | 602 | Linear | 0.32 (0.07, 0.64) | <0.001 | 0.4 | 0.288 | 0.444 | | Large (≥10 mm) | 279 | Linear | 1.76 (0.78, 3.74) | <0.001 | 0.098 | 0.355 | 0.462 | | *Nodule behavior and size* |  |  |  |  |  |  |  | | Non-neoplastic, <10 mm | 463 | Linear | 0.13 (<0.51, 0.43) | 0.012 | 0.064 | >0.5 | 0.086 | | Non-neoplastic, ≥10 mm | 113 | Linear | 2.19 (0.72, 7.01) | 0.004 | >0.5 | 0.09 | 0.179 | | Neoplastic, <10 mm | 28 | Linear | 1.99 (<0.07, 30.12) | 0.02 | 0.19 | 0.072 | NE | | Neoplastic, ≥10 mm | 73 | Linear | 2.41 (0.27, 11.77) | 0.033 | >0.5 | >0.5 | >0.5 | | *Singularity* |  |  |  |  |  |  |  | | Single | 648 | Linear | 0.56 (0.26, 0.96) | <0.001 | 0.311 | >0.5 | >0.5 | | Multiple | 233 | Linear | 0.59 (0.07, 1.84) | <0.001 | 0.08 | 0.02 | 0.09 | |  |  | Lin-exp\* | 0.22 (<-0.09, 1.11); 0.09 (0.11, 0.18) |  |  |  |  | | **Dose range: 0 to 5 Gy** | | | | | | | | |  |  | **EOR (95% CI)/Gy, βdose1** | | **P-values2** | | | | |  | **N** |  |  | **Age at** |  | **Lin-** | **Lin-** | | **Type of nodule** | **cases** | **Model** | **Linear term, β** | **accident** | **Sex** | **exp** | **quad** | | All nodules | 852 | Linear | 0.70 (0.33, 1.18) | <0.001 | >0.5 | 0.486 | >0.5 | | *Nodule behavior* |  |  |  |  |  |  |  | | Non-neoplastic, all | 559 | Linear | 0.33 (<0.04, 0.70) | 0.016 | 0.155 | >0.5 | >0.5 | | Not referred for FNB/surgery | 442 | Linear | 0.11 (-0.08, 0.41) | 0.375 | DNC | DNC | DNC | | Confirmed non-neoplastic | 117 | Linear | 1.83 (<0.25, 5.96) | 0.012 | >0.5 | 0.414 | 0.499 | | Suspicious | 195 | Linear | 1.55 (0.36, 4.42) | <0.001 | 0.06 | 0.149 | 0.236 | | Neoplastic | 91 | Linear | 3.83 (0.89, 15.45) | 0.002 | 0.19 | >0.5 | >0.5 | | *Nodule size* |  |  |  |  |  |  |  | | Small (<10 mm) | 586 | Linear | 0.27 (<0.07, 0.71) | 0.002 | 0.222 | 0.178 | 0.171 | | Large (≥10 mm) | 266 | Linear | 2.13 (0.97, 4.59) | <0.001 | 0.059 | >0.5 | >0.5 | | *Nodule behavior and size* |  |  |  |  |  |  |  | | Non-neoplastic, <10 mm | 455 | Linear | 0.02 (<0.02, 0.48) | 0.055 | DNC | >0.5 | >0.5 | | Non-neoplastic, ≥10 mm | 104 | Linear | 1.63 (0.39, 5.68) | 0.077 | DNC | >0.5 | >0.5 | | Neoplastic, <10 mm | 25 | Linear | 3.41 (<0.60, 76.04) | 0.02 | 0.133 | 0.133 | DNC | | Neoplastic, ≥10 mm | 71 | Linear | 4.20 (1.02, 21.13) | 0.015 | >0.5 | >0.5 | >0.5 | | *Singularity* |  |  |  |  |  |  |  | | Single | 627 | Linear | 0.67 (0.30, 1.19) | <0.001 | 0.117 | 0.428 | >0.5 | | Multiple | 225 | Linear, all | 0.61 (<0.23, 2.03) | 0.001 | 0.005 | >0.5 | >0.5 | |  |  | Linear,  sex-specific\* | 0.10 (<0.61, 3.60) in men 1.40 (<-0.22, 3.59) in women |  |  |  |  | |

Abbreviations: EOR, excess odds ratio; CI, confidence interval; Gy, gray; Lin-exp, linear-exponential model for dose; Lin-quad, linear-quadratic model for dose; FNB, fine needle biopsy; DNC, did not converge.

\* Indicates best fitting model when more than one model is presented.

1 All models adjusted for sex, log age at screening, urban status at screening, oblast of residence at screening (Minsk, Gomel, Other), diffuse goiter detected during screening, any family history of thyroid disease, enlarged thyroid volume (defined as thyroid volume >18 ml for women and >25 ml for men) and centered for participants aged 5 at time of the accident.

2 P-values based on likelihood ratio tests with models adjusted for all factors described above and an age at time of accident interaction term.

## Table S2. Effect modification of the excess odds ratio of prevalent thyroid nodules per gray of I-131 according to selected characteristics, 0 to < 5 Gy.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | |  |  | **Excess Odds Ratio per Gy (95% Confidence Interval)1** | | | | | | | | **Modifying factor** | **Cases2** | **All nodules** | **Non-neoplastic** | **Neoplastic** | **Small (<10 mm)** | **Large (≥10 mm)** | **Single** | **Multiple** | |  |  |  |  |  |  |  |  |  | | All participants | 852 | 0.44 (0.26, 0.67) | 0.22 (0.05, 0.43) | 1.76 (0.71, 4.13) | 0.23 (0.06, 0.46) | 0.95 (0.52, 1.59) | 0.44 (0.24, 0.70) | 0.42 (0.12, 0.87) | | Sex |  |  |  |  |  |  |  |  | | Male | 335 | 0.45 (0.20, 0.81) | 0.10 (NE, 0.38) | 3.45 (0.95, 15.6) | 0.25 (0.01, 0.59) | 1.06 (0.41, 2.29) | 0.63 (0.29, 1.13) | 0.06 (NE, 0.52) | | Female | 517 | 0.43 (0.20, 0.74) | 0.33 (0.08, 0.67) | 1.07 (0.24, 3.20) | 0.22 (0.01, 0.53) | 0.88 (0.38, 1.69) | 0.30 (0.08, 0.61) | 0.80 (0.29, 1.67) | | P for interaction |  | > 0.50 | 0.22 | 0.16 | > 0.50 | > 0.50 | 0.15 | 0.03 | | Urban status at time of the accident | | | | | | | | | | Rural | 524 | 0.47 (0.28, 0.72) | 0.25 (0.07, 0.48) | 1.86 (0.75, 4.31) | 0.26 (0.08, 0.51) | 0.98 (0.52, 1.66) | 0.47 (0.25, 0.76) | 0.45 (0.14, 0.92) | | Urban | 328 | 0.28 (NE, 0.67) | 0.05 (NE, 0.45) | 1.10 (NE, 4.14) | 0.07 (NE, 0.47) | 0.80 (0.15, 1.85) | 0.30 (0.00, 0.75) | 0.19 (NE, 1.06) | | P for interaction |  | 0.30 | 0.29 | 0.44 | 0.31 | > 0.50 | 0.42 | 0.48 | | Oblast of residence at time of the accident3 | | | | | | | | | | Minsk | 104 | NE | NE | 1.03 (0.02, 10.6) | NE | NE | NE | 0.01 (0.00, > 8.78) | | Gomel | 684 | 0.43 (0.25, 0.67) | 0.22 (0.05, 0.45) | 2.23 (0.90, 5.28) | 0.21 (0.04, 0.44) | 1.02 (0.55, 1.74) | 0.43 (0.22, 0.70) | 0.43 (0.11, 0.91) | | Other | 64 | 0.53 (NE, 1.55) | 0.30 (NE, 1.50) | NE | 0.20 (NE, 1.44) | 1.15 (0.05, 3.45) | 0.55 (NE, 1.76) | 0.57 (NE, 3.09) | | P for interaction |  | 0.18 | 0.46 | 0.08 | 0.41 | 0.31 | 0.19 | > 0.50 | | Urinary iodine concentration, μg/L4 | | | | | | | | | | 0 to 19 | 109 | 0.89 (0.33, 1.92) | 0.75 (0.11, 2.09) | 4.42 (0.51, > 42.7) | 0.63 (0.05, 1.84) | 1.21 (0.31, 3.61) | 0.74 (0.18, 1.86) | 1.31 (0.21, 4.79) | | 20 to 99 | 453 | 0.46 (0.22, 0.77) | 0.15 (NE, 0.42) | 1.47 (0.40, 4.33) | 0.23 (0.02, 0.54) | 1.04 (0.46, 2.04) | 0.50 (0.22, 0.90) | 0.33 (NE, 0.90) | | 100 to 2120 | 282 | 0.23 (0.00, 0.58) | 0.20 (0.00, 0.59) | 1.60 (0.14, 8.41) | 0.12 (NE, 0.49) | 0.57 (0.05, 1.62) | 0.23 (NE, 0.62) | 0.22 (NE, 1.05) | | P for interaction |  | 0.15 | 0.26 | > 0.50 | 0.37 | > 0.50 | 0.31 | 0.28 | | Thyroid enlargement5 | | | | | | | | | | No | 723 | 0.43 (0.24, 0.68) | 0.22 (0.05, 0.44) | 1.52 (0.54, 3.77) | 0.23 (0.05, 0.46) | 1.03 (0.53, 1.82) | 0.48 (0.25, 0.77) | 0.29 (0.01, 0.73) | | Yes | 129 | 0.43 (0.03, 1.17) | 0.20 (NE, 1.03) | 4.23 (0.39, > 25.1) | 0.27 (NE, 1.22) | 0.59 (0.04, 1.89) | 0.20 (NE, 0.91) | 1.00 (0.15, 3.07) | | P for interaction |  | > 0.50 | > 0.50 | 0.41 | > 0.50 | 0.43 | 0.37 | 0.18 | | Diffuse goiter detected during screening6 | | | | | | | | | | No | 572 | 0.33 (0.15, 0.57) | 0.20 (0.02, 0.45) | 1.02 (0.23, 2.94) | 0.25 (0.06, 0.51) | 0.54 (0.16, 1.16) | 0.34 (0.13, 0.62) | 0.28 (NE, 0.76) | | Yes | 279 | 0.45 (0.16, 0.90) | 0.09 (NE, 0.45) | 2.72 (0.66, 13.3) | 0.003 (0.00, 0.37) | 1.17 (0.48, 2.47) | 0.46 (0.12, 0.99) | 0.47 (0.01, 1.36) | | P for interaction |  | > 0.50 | > 0.50 | 0.25 | 0.19 | 0.18 | > 0.50 | > 0.50 | | Any family history of thyroid disease7 | | | | | | | | | | No | 721 | 0.40 (0.22, 0.63) | 0.19 (0.02, 0.41) | 2.14 (0.82, 5.52) | 0.20 (0.03, 0.42) | 0.94 (0.48, 1.65) | 0.40 (0.20, 0.67) | 0.37 (0.07, 0.85) | | Yes | 110 | 0.76 (0.17, 1.90) | 0.47 (NE, 1.71) | 0.13 (NE, 2.62) | 0.78 (0.04, 2.46) | 0.72 (NE, 2.61) | 0.86 (0.11, 2.56) | 0.62 (NE, 2.53) | | P for interaction |  | 0.32 | 0.44 | 0.10 | 0.18 | > 0.50 | 0.33 | > 0.50 | |

Abbreviation: Gy, gray.

1 All models adjusted for sex, log age at screening, and urban status at screening.

2 Numbers may be inconsistent due to missing values for iodine concentration, diffuse goiter detected during screening, and any family history of thyroid disease.

3 Additionally adjusted for oblast at screening.

4 Additionally adjusted for urinary iodine categories (0 to 19, 20 to 99, 100-2120 μg/L).

5 Additionally adjusted for thyroid enlargement defined as thyroid volume >18 ml for women and >25 ml for men.

6 Additionally adjusted for diffuse goiter detected during screening.

7 Additionally adjusted for any family history of thyroid disease reported at screening.