Endocrine Diseases in Post-Chernobyl Period in Belarus

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26 April 1986
The accident at the Chernobyl nuclear power plant

Radioactive substance release - 13 EBq:
- $^{131}$I - 1.8 Ebq
- $^{137}$Cs - 0.085 Ebq
- $^{90}$Sr - 0.01 Ebq
- Pu isotopes - 0.003 EBq

More than 200 000 sq km of Europe were contaminated with > 37 kBq/sq m of $^{137}$Cs.

Over 70 % of this area was in the three most affected countries, Belarus, Russia and Ukraine.

The Chernobyl Forum: 2003-2005, IAEA
The accident at the No. 4 reactor of the Chernobyl Power Station took place on April 26, 1986, at 1:23 AM.

Two explosions occurred, the first due to steam and a second one due to hydrogen. The explosions expelled fission products and fuel elements to the exterior that accumulated in a cloud reaching to approximately 7,000 m and centered at approximately 4,500 m.

Because the graphite ignited, there was a second, more prolonged but less intense, release over a 9- to 10 day period that peaked on May 6, 1986, and dropped sharply on May 11 as the fire was extinguished. The following volatile elements, as well as the noble gases xenon and krypton, constituted the most abundant released material: Iodine, cesium, and tellurium.
INTRODUCTION

• Republic of Belarus belongs to European countries with predominantly light and moderate chronic iodine deficiency

• The State Program of iodine prophylaxis with iodinated salt or KI tablets was stopped in the end of 70-s yrs. and restored - during 1998-2000 yrs. (12 yrs. after the Chernobyl catastrophe);

• There were no organized prophylaxis with stable iodine among the population during first hours/days/weeks of the Chernobyl catastrophe;
• Starting a week after the Accident and then - during all summer months in 1986yr. there was spontaneous individual intake of iodine solutions in different doses by different age group of population

• Side effects:
  • Rashes
  • very firm thyroid gland, autoimmune thyroiditis
  • Wolf-Chaickoff effects
In Poland, decided to adopt the very conservative dose commitment - increased air radioactivity was first detected on the of 50 mSv as the intervention level for children.

The commission on the morning of April 29: Whole body committed dose should not exceed 5 mSv/y (0.5 rem). Thyroid committed dose should not exceed 50 and amounted to 504 Bq of radioiodines /m3 air with 1.55- to 3.0×times higher values in northeast Poland. Approximately 18 million doses of KI solution were sources distributed;

“95.3% of children received iodide prophylaxis;
86.7% took a single dose,
2.39% took two or more doses,
and a surprising 6.14% were given diluted tincture of iodine by their parents before the start of the program and then took a single dose of KI”
Approximately 10.5 million children 16 years old and under, and approximately 7 million adults received iodide prophylaxis in Poland.

**IODIDE PROPHYLAXIS IN POLAND AFTER THE CHERNOBYL REACTOR ACCIDENT: BENEFITS AND RISKS**

Distribution of Iodine-131 in the Soil
(May 10, 1986)
Belarusian territory: contamination with Cesium-137, Strontium-90 and Plutonium-238, 239, 240 (January 1, 1995)
**Effect of chronic iodine deficiency and stable iodine consumption**

**Table 4.** Estimated risk of developing thyroid cancer after a radiation dose of 1 Gy, by level of soil iodine in the settlement of residence at the time of the accident and by potassium iodide (i.e., antistrumin) consumption status (analyses restricted to subjects with radiation doses to the thyroid of less than 2 Gy)*

<table>
<thead>
<tr>
<th>Consumption of potassium iodide</th>
<th>OR at 1 Gy (95% CI)</th>
<th>Highest two tertiles of soil iodine</th>
<th>Lowest tertile of soil iodine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>3.5 (1.8 to 7.0)</td>
<td></td>
<td>10.8 (5.6 to 20.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.1 (0.3 to 3.6)</td>
<td></td>
<td>3.3 (1.0 to 10.6)</td>
</tr>
</tbody>
</table>

*Levels of iodine in soil in settlement of residence at time of accident were divided into tertiles. OR = odds ratio at 1 Gy compared with no exposure; CI = confidence interval.

Cardis 2005
Exposure to ionizing radiation is the only established risk factor of thyroid cancer in early childhood


Tab. 2. Excess relative risk for thyroid carcinoma. Comparing Chernobyl to external radiation, and comparing the effect of iodine intake on the risk (5)

<table>
<thead>
<tr>
<th>Chernobyl overall</th>
<th>External radiation</th>
<th>Chernobyl high iodine</th>
<th>Chernobyl low iodine</th>
<th>Chernobyl high I + KI</th>
<th>Chernobyl low I + KI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERR</td>
<td>4,5-7,4</td>
<td>7,7</td>
<td>2,5</td>
<td>9,8</td>
<td>0,1</td>
</tr>
</tbody>
</table>
Screening for Chernobyl-associated disorders in Belarusian population started in May 1986
## Screening data of thyroid nodules and thyroid cancer in Belarus after the Chernobyl accident

<table>
<thead>
<tr>
<th>Screening programs</th>
<th>Year of screening</th>
<th>N of subjects</th>
<th>Diseases</th>
<th>Thyroid nodes</th>
<th>Thyroid carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP, IAEA (Mettler et al, 1992)</td>
<td>1990</td>
<td>323</td>
<td></td>
<td>4</td>
<td>1,24</td>
</tr>
<tr>
<td>Screenign program of Research</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Institute of Radiation Medicine, Choiniki, Gomel oblast, Belarus (Drozd et al., 1993, Drozd et al., 2002)</td>
<td>1990-1991</td>
<td>1132</td>
<td></td>
<td>14</td>
<td>1,24</td>
</tr>
<tr>
<td></td>
<td>1993</td>
<td>1546</td>
<td></td>
<td>32</td>
<td>2,1</td>
</tr>
<tr>
<td>Chernobyl Sasakawa Project. Sasakawa Memorial Health Foundation (Yamashita, 1999)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mogilev oblast</td>
<td></td>
<td>13868</td>
<td></td>
<td>24</td>
<td>0,1</td>
</tr>
<tr>
<td>Gomel oblast</td>
<td></td>
<td>19790</td>
<td></td>
<td>350</td>
<td>1,7</td>
</tr>
<tr>
<td>A Cohort study of Thyroid cancer and thyroid diseases after the Chernobyl Accident.</td>
<td>1996-2001</td>
<td>11200</td>
<td></td>
<td>694</td>
<td>6,2 n/I</td>
</tr>
<tr>
<td>Chernobyl disease study group of Belarus and USA</td>
<td>2004</td>
<td>25 161</td>
<td></td>
<td>n/I</td>
<td>n/I</td>
</tr>
<tr>
<td>Ostapenko et al., 2001</td>
<td></td>
<td>694</td>
<td></td>
<td>6,2 n/I</td>
<td>53</td>
</tr>
<tr>
<td>Stezhko V. et al. 2004</td>
<td></td>
<td>161</td>
<td></td>
<td>0,47</td>
<td></td>
</tr>
<tr>
<td>Screening project of Red Cross (Brest oblast) (unpublished data)</td>
<td>1998-2008</td>
<td>164175</td>
<td></td>
<td>23693</td>
<td>14,4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>499</td>
<td>0,3</td>
</tr>
</tbody>
</table>
Dynamics of the measured daily
Deposition Density of 131I in the Cities
of Brest Oblast

Yu. Gavrilin, S. Shinkarev, A. Bouville, M. Germenchuk, M. Hoshi, N. Luckyanov, P.
Voilleque, O. Zhukova «Retrospective Assessment Of Thyroid Doses For The Residents Of Brest Oblast Of Belarus», 2004
Screening in Stolin Brest region (1996-2008)
• In 2000-2011 active screening for thyroid diseases was performed in women of reproductive age in Minsk and Brest regions
  – Percentage of women with individual levels of TSH between 2.5-3.5 mIU/l was 48.7%, 3.5-4.5 mIU/l – 9.4%, > 4.5 mIU/l – 8.2%
  – Ultrasound abnormalities of thyroid gland were revealed in 44.6% examined women (among them – 23.4% were TPO-Ab positive)
• 2000-2002 fT4 and TSH-screening in pregnant women revealed non optimal distribution of individual levels during first 9 weeks of pregnancy
• Next fT4 and TSH-screening was performed in pregnant women (9 weeks of pregnancy) in 2009-2011 yrs
Distribution of the cases of different TSH levels in women during first 9 weeks of pregnancy (2000-2002)

N=316

E.M.Kapustina et al., 2002.
Distribution of the cases of different TSH levels in women during first 9 weeks of gravities (2009-2011)

N=290

Distribution of TSH levels in women during first 9 weeks of gravities:

- 0.5-1.0 mIU/l: 10 (3.45%)
- 1.1-2.5 mIU/l: 120 (41.38%)
- 2.5-3.5 mIU/l: 130 (44.83%)
- 3.5-4.5 mIU/l: 30 (10.34%)

Total: N=290
Iodine excretion screening in Brest and Minsk regions

• According to results of screening in some districts of Brest and Minsk regions - the situation is changing to the best.
  – The median levels of iodine excretion in Stolin (Brest region) in 2002 yr were 36.4 μg/L (18.3 / 47.5) in adults and 43.6 μg/L in schoolchildren.
  – In Minsk region median levels of iodine excretion during the same period were 59.8 μg/L in adults and 75.4 μg/L - in schoolchildren.

• In 2007 yr the median level of iodine excretion in children of
  – Stolin reached 76.3 μg/L
  – Minsk region - 73.2 μg/L.
Congenital Hypothyroidism

Screening programs for congenital hypothyroidism
Thyroid tests and Prophylaxis with stable iodine during pregnancy
Autoimmune thyroiditis

- Increased incidence of autoimmune endocrine diseases in children and adolescents (Autoimmune thyroiditis during 1995-2000 yrs.)
- Clinical features of autoimmune thyroiditis in groups of patients under 25 yrs. – subclinical forms and coexistence with nodular pathology, coexistence with DM type 1;
- Retardation/ impairments of physical and sexual development in children and adolescents
Possible Etiologic Factors of Thyroid Diseases

Endogenous factors
- Gender
- Age
- Ethnic factors
- Hormones
- Pregnancy

Exogenous factors
- Diet
- Pollutants
- Infections
- Drugs
- Smoking
- Irradiation

Genetic factors
- BRAF
- RET/PTC
- HLA
- non-HLA
- CTLA-4
- AIRE
Thyroid nodules in clinical practice

Their prevalence depends to a great extent on the method used for detection. With the increased utilization of US for evaluation of the lesions of the neck, the incidental finding of unsuspected thyroid nodules has dramatically increased. The prevalence of thyroid nodules is higher in women in areas of iodine deficiency and increases with advancing age.

Factors that increase the risk of malignancy include radiation exposure, history of head and neck irradiation, and very young or advanced age.

Nodular Goiter / Incidence rate
Statistical data of the Ministry of Public Health

Nodular Goiter in adults - cases per 100,000 persons
Nodular thyroid disease
### Incidence of thyroid cancer diagnosed in 1986-2002

<table>
<thead>
<tr>
<th>Age at exposure (yr)</th>
<th>Belarus</th>
<th>Russian Federation</th>
<th>Ukraine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>1,711</td>
<td>349</td>
<td>1,762</td>
<td>3,822</td>
</tr>
<tr>
<td>15-17</td>
<td>299</td>
<td>134</td>
<td>582</td>
<td>1,015</td>
</tr>
<tr>
<td>Total</td>
<td>2,010</td>
<td>483</td>
<td>2,344</td>
<td>4,837</td>
</tr>
</tbody>
</table>

*Health Effects of the Chernobyl Accident and Special Health Care Programmes / Report of the UN Chernobyl Forum, 2006*

UNSCEAR 2008 Report, Annex D: Over 6,000 thyroid cancers by 2006
There has been a great increase in the incidence of thyroid cancer and benign thyroid nodules following the release of radioiodine by the Chernobyl accident, which occurred on 26 April 1986. Less thoroughly evaluated has been the prevalence of thyroid autoimmunity, even though external irradiation is recognized to increase the incidence of autoimmune thyroiditis. The Belarus-USA Study was established to quantitate the risk of thyroid and parathyroid disease in a well-defined cohort of individuals under age 18 years at the time of the accident who had direct thyroid radiation measurements. Subjects are examined at least biennially and undergo diagnostic procedures including thyroid palpation and ultrasound (US) and assay of serum for thyroid antibodies, TSH, free T4, and thyroglobulin. By 1 October 2000, 9400 cohort members have been screened at least once.
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Central Lab
Blood testing:
TSH, ABTPO, ABTG, FT4, Ca2+
Urine tests:

Endocrinologist (palpation)

Ultrasound examination (palpation)

Dosimetry interview

Blood and urine collection.

Referrals

Biennial examination

Results

FNA

Endocrinology department

Histopathology

Oncopathology Center

FINAL CONCLUSION
## PREVALENCE OF ANTITHYROID ANTIBODIES IN EXPOSED SUBJECTS OF BELARUS AND RUSSIA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BelAm</th>
<th>Sasakawa Project</th>
<th>F.Pacini et al., 1998</th>
<th>F.Vermiglio et al., 1999</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in 1986, years</td>
<td>0 - 18</td>
<td>0 - 10</td>
<td>&lt;1 - 10</td>
<td>In utero - 3</td>
</tr>
<tr>
<td>Age at examination, years</td>
<td>11 - 32</td>
<td>5 - 20</td>
<td>6 - 17</td>
<td>5 - 15</td>
</tr>
<tr>
<td>Prevalence of ABTPO</td>
<td>5.8%</td>
<td>2.5%</td>
<td>16.7%</td>
<td>18.9%</td>
</tr>
<tr>
<td>Prevalence of ABTG</td>
<td>4.9%</td>
<td>1%</td>
<td>8.4%</td>
<td>12.6%</td>
</tr>
</tbody>
</table>
*All diagnoses but thyroid cancer made according to preliminary endocrinological conclusion. Thyroid cancer pathologically confirmed

Y axis - % AB(+)
Consequences of Chernobyl Accident

Measures of Thyroid Function among Belarusian Children and Adolescents Exposed to Iodine-131 from the Accident at the Chernobyl Nuclear Plant

Eugenia Ostrovna,1 Alexander Rozhko,2 Maureen Hatch,1 Kyoko Furukawa,2 Olga Polyaniksa,2 Robert J. McConnell,3 Eldar Nadaryov,4 Sergey Petrenko,5 Georgie Romanov,5 Veselina Yanovsky,5 Vladimir Dolgivtov,5 Viktor Minkevich,5 Alexander Prokopenovich,4 Irina Savastova,5 Lyuba B. Zabotkina,4 Kiyohiko Mizobuchi, and Alla V. Brenner1

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BACKGROUND: Thyroid dysfunction after exposure to low to moderate doses of radioactive iodine-131 (131I) by a young age is a public health concern. However, quantitative data are sparse concerning 131I-related risk of three common diseases.

OBJECTIVE: Our goal was to assess the prevalence of thyroid dysfunction in association with 131I exposure during childhood (≤18 years) due to fallout from the Chernobyl accident.

METHODS: We conducted a cross-sectional analysis of hyperthyroidism, hypothyroidism, autoimmune thyroiditis (AIT), serum concentrations of thyroid-stimulating hormone (TSH), and antimicrobial antibodies to thyrotropin receptor (ATPO) in relation to measurement-based 131I dose estimates in a Belarusian cohort of 1033 individuals screened for various thyroid diseases.

RESULTS: Mean age at exposure (±SD) was 8.7 ± 5.0 years. Mean (median) estimated 131I thyroid dose was 0.54 (0.23) Gy. Yields (0.80–26.6 Gy) were found for positive associations of 131I with hyperthyroidism (mainly subclinical and antibody-negative) and serum TSH concentration. The mean value for one Gy for hyperthyroidism was 0.0091% (95% CI 0.15% 0.05%) and varied significantly by age at exposure and at examination, presence of maternal, and urban/rural residence. We found an inverse association with antithyroid antibodies (hyperthyroidism, hypothyroidism, AIT, or elevated ATPO).

CONCLUSION: The association between 131I dose and hyperthyroidism in the Belarusian cohort is consistent with that previously reported for a Ukrainian cohort and strengthensthe effect of environmental 131I exposure during childhood on hyperthyroidism, but not on other thyroid outcomes.

KEY WORDS: antithyroid antibodies, autoimmune thyroiditis, Chernobyl, children, thyroid dose, exposure, hyperthyroidism, hypothyroidism, radioactivity, thyroid gland.


The most severe accident in the history of nuclear industry occurred on 26 April 1986, evidence of a decline in radiation-related risk of thyroid cancer (Brenner et al., 2011). ...
Thyroid cancer

- Current Belarusian guidelines for the treatment of progressive DTC include optimization of TSH suppression, 131I, resection of selected metastases, bisphosphonates for bony metastases (Y. Demidchik, L.Danilova, V.Drozd, M.Lushchyk, 2010);

- Like the RET/PTC, mutations in BRAF are thought to occur early in thyroid cancers tumorigenesis (Nikiforova et al. 2003) and discussed as an attractive target for molecular therapies.
Nodular Goiter / Incidence
adolescents
Statistical data of the Ministry of Public Health

Nodular Goiter in adolescents - cases per 100 000 persons


Minsk

Brest oblast

Vitebsk oblast

Gomel oblast

Grodno oblast

Minsk oblast

Mogilev oblast

Belarus
Distribution of total amount of patients with Thyroid Cancer in different regions of Belarus 1990-2011 (21,616 cases)
Yearly number of patients with thyroid cancer in Belarus: 1990 to 2011

Statistical data of the Ministry of Public Health
Thyroid Cancer in Children and Teenagers

(E.P. Demidchik et al., 2002-2004)
Thyroid cancer: Age-dependent incidence

(Y. Demidchik et al., 2012)
Thyroid cancer in the regions of Belarus
Standardized Incidence Rate
(per 100 000 people)
Statistical data of the Ministry of Public Health
Thyroid cancer: Mortality and Incidence rate

Statistical data of the Ministry of Public Health

Graph showing the trend of mortality and incidence rates from 1990 to 2010.
Thyroid cancer: mortality since 1990, absolute number of cases (normalized graph) (Y. Demidchik et al, 2012)
Thyroid cancer: mortality, total number of deceased 1990-2013

Statistical data of the Ministry of Public Health
Yearly number of patients with thyroid cancer 1990-2011 in Belarus

Statistical data of the Ministry of Public Health
Distribution of Thyroid Cancer cases in different age groups according to TNM stages
Brest region  n=2005 / Brest Regional Dispensary statistic data
Percentage ratio of different morphological variants of thyroid cancer in Brest region 1990-2013

Brest Regional Dispensary statistic data

<table>
<thead>
<tr>
<th>Variant</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary</td>
<td>93.8%</td>
</tr>
<tr>
<td>Follicular</td>
<td>2.2%</td>
</tr>
<tr>
<td>Medullary</td>
<td>1.4%</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>1.4%</td>
</tr>
<tr>
<td>Other</td>
<td>1.2%</td>
</tr>
</tbody>
</table>
Distribution of Thyroid Cancer cases in different age groups according to TNM stages in the Brest region (n=2000)
Distribution of Thyroid Cancer cases in different age groups according to TNM stages In Brest region

n=1965
Thyroid average and collective doses /131-Iodine and number of thyroid cancer cases in Republic of Belarus

<table>
<thead>
<tr>
<th>Contaminated territory</th>
<th>Average dose (mGy)</th>
<th>Collective dose</th>
<th>Number of Thyroid Cancer cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-7 years</td>
<td>14-18 years</td>
<td>adults</td>
</tr>
<tr>
<td>Minsk oblast</td>
<td>22,9</td>
<td>7,1</td>
<td>7,4</td>
</tr>
<tr>
<td>Gomel oblast</td>
<td>475,8</td>
<td>145,0</td>
<td>148,1</td>
</tr>
<tr>
<td>Mogilev oblast</td>
<td>97,6</td>
<td>29,4</td>
<td>30,7</td>
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<tr>
<td>Brest oblast</td>
<td>77,8</td>
<td>23,9</td>
<td>24,7</td>
</tr>
<tr>
<td>Grodno oblast</td>
<td>16,7</td>
<td>5,2</td>
<td>5,4</td>
</tr>
<tr>
<td>Vitebsk oblast</td>
<td>5,5</td>
<td>1,6</td>
<td>1,7</td>
</tr>
<tr>
<td>Belarus</td>
<td>122</td>
<td>37</td>
<td>37</td>
</tr>
</tbody>
</table>


Thyroid cancer in Belarus

• The incidence of thyroid cancer in children is likely to be decreased;
  – 2007 - 11 newly diagnosed cases,
  – 2010 – 11 cases,
  – 2011 - 19 cases;

• The incidence of thyroid cancer among older age groups of population is increasing
  – 1993 – 484 cases
  – 2010 – 1098 cases
  – 2011 - 1165
Fig. The incidence of well differentiated thyroid cancer (WDTC) over time is illustrated for all patients and for low risk patients.

Gopalakrishna Iyer N, Morris L, Michael Tuttle R, Shaha A, Ganly I, Rising Incidence of Second Cancers in Patients With Low-Risk (T1N0) Thyroid Cancer Who Receive Radioactive Iodine Therapy. Cancer 2011; Published online in Wiley Online Library (wileyonlinelibrary.com)
New surgical technologies in Nodular Thyroid disease
Conservative Treatment of Thyroid Nodular Disease

- New ablation technologies in Nodular Thyroid diseases
Thyroid nodules


- **BRAF** is a non-receptor serine threonine kinase involved in the RAS/RAF/MAPK/ERK signaling cascade.
Personalized Thyroidology

- Personalized prophylaxes
- Personalized diagnosis
- Personalized treatment
- Personalized prognosis
Epigenetic therapy and prophylaxes

- The complexity of human carcinogenesis cannot be accounted for by genetic alterations alone, but also involves epigenetic changes in processes such as DNA methylation, histone modifications, and microRNA expression.

- In turn, these molecular alterations lead to permanent changes in the expression of genes that regulate the neoplastic phenotype, such as cellular growth and invasiveness.

- Targeting epigenetic modifiers has been referred to as epigenetic therapy

Thyroid cancer in Belarus: Personalized prognosis, diagnosis and treatment

- Environmental chemicals
- Drugs/Pharmaceuticals
- Combined effect of radiation exposure and environmental factors
- Development in utero and in childhood
Conclusion

- Continuation of active screening programs in contaminated and non-contaminated regions of Belarus are required to elucidate the prevalence of widespread thyroid dysfunctions, early detection of thyroid cancer in high-risk groups (those who had radiation exposure to the thyroid gland in utero and childhood, people living in the areas around Chernobyl or moved to other places after they had received radiation doses), and verified influence of endocrine disrupters in modifying epigenetic mechanisms or potentiate the carcinogenic effect of radiation exposure.
Acknowledgments

Belarusian Medical Academy of Postgraduate Education:
• V. Drozd
• M. Lushchyk
• A. Romanovsky
• G. Panasuk

Republican Military Medical Center 432
V. Valuevitch

Regional Endocrinology Dispensaries:
• A. Grigorovitch
• V. Sivuda
• M. Tulupova
• V. Selivanov

Republican Endocrinology Dispensary
• S. Korytko
• E. Gapanovitch

Republican Oncology Center
• Y. Averkin