THYROID CANCER IN UKRAINE AFTER THE CHORNOBYL DISASTER: THE CURRENT ACHIEVEMENTS AND STRATEGY OF FURTHER RESEARCH

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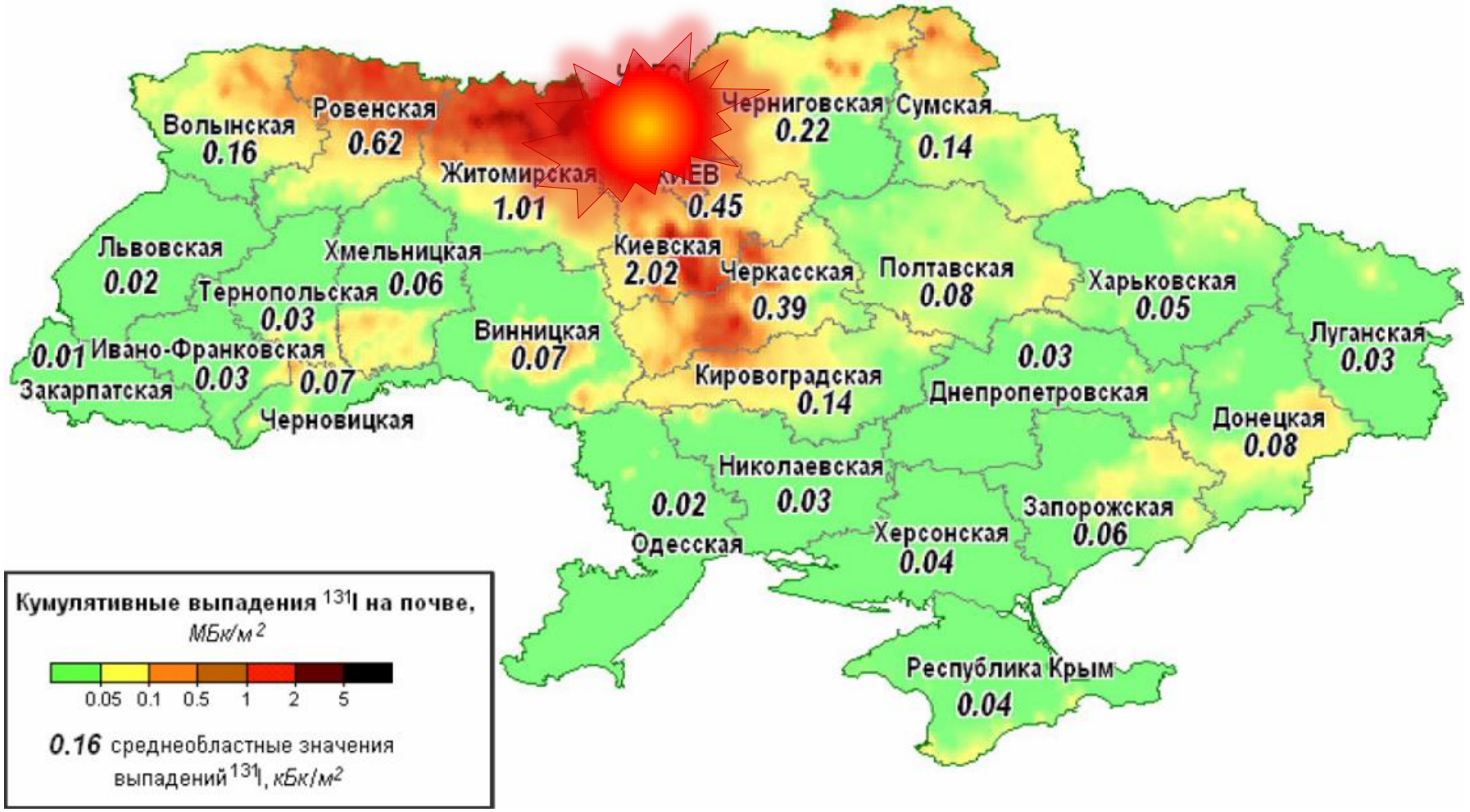
Comparison of radioactive iodine I^{131} fallout from nuclear reactors

Episode	I^{131} fallout (Curie)
Accident at Three Mile Island Nuclear Power Station, USA (1979)	15-20
Accident at the reactor "Windscale", UK (1957)	20 000
Technological fallout from a reactor in the process of plutonium production at the enterprise in Hanford, Washington, USA.	690 000
Accident at Chernobyl Nuclear Power Station, Ukraine (1986)*	40 000 000 – 50 000 000
Accident at Fukushima Nuclear Power Station, Japan (2011)**	4 000 000 – 5 000 000

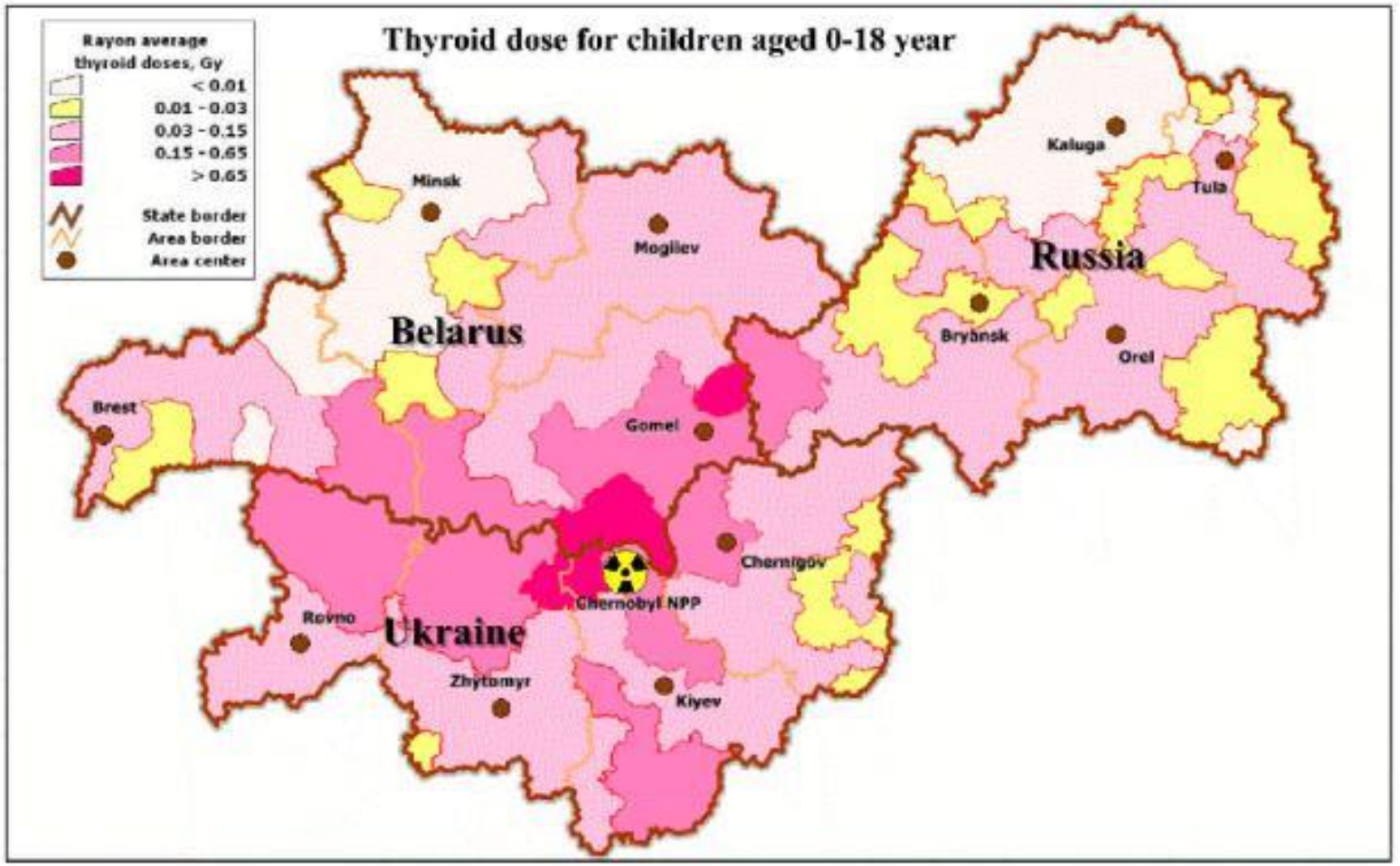
* In addition, fallouts of short-lived iodine and tellurium isotopes are estimated to be equal to 100,000,000 Curie (UNSCEAR 2008).

** Report of Japanese Government to IAEA Ministerial Conference on Nuclear Safety - Accident at TEPCO's Fukushima Nuclear Power Stations, 7 June 2011.

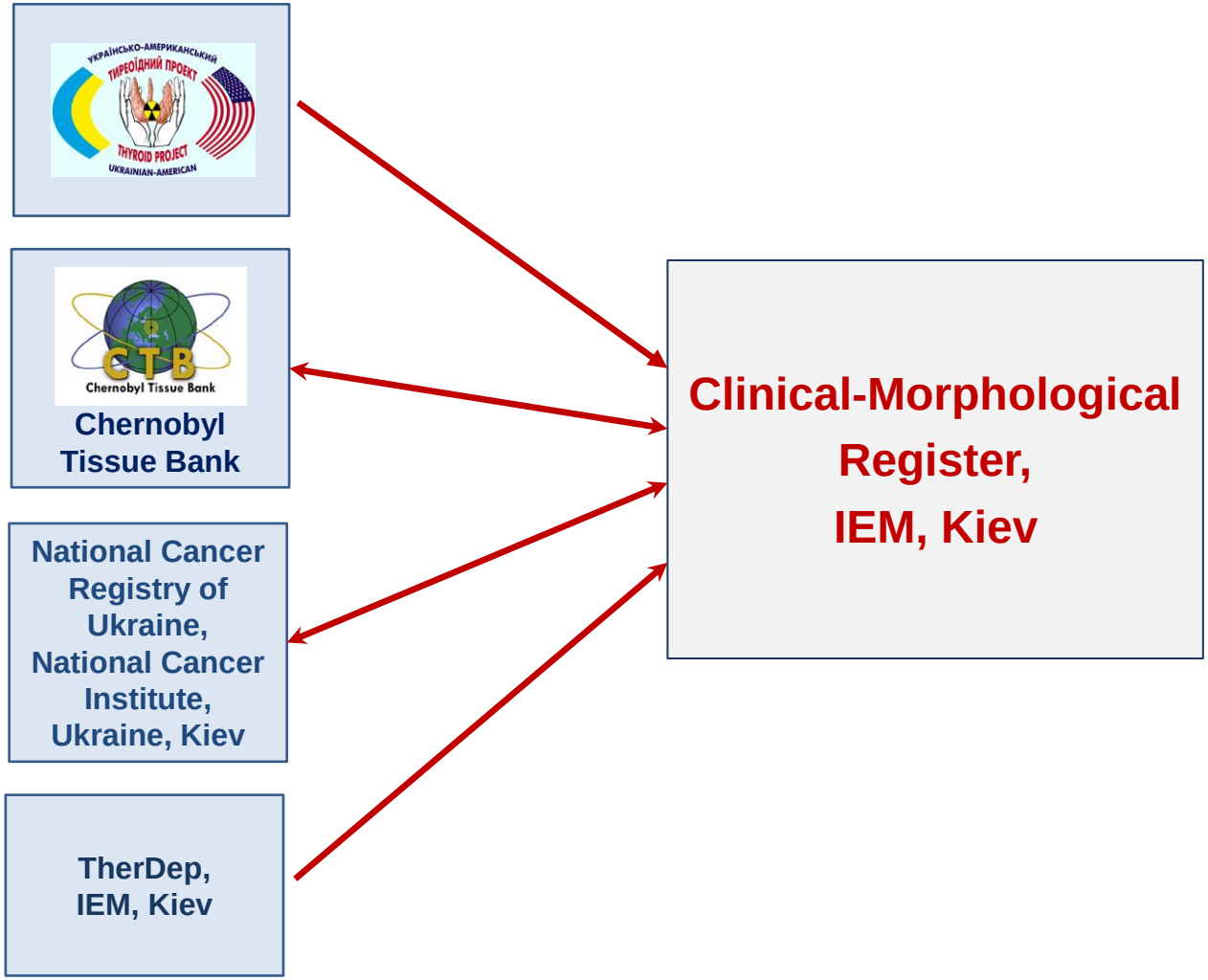
Cumulative fallout of I^{131} in the territory of Ukraine as a result of the Chernobyl accident (April 26th– May 7th, 1986)



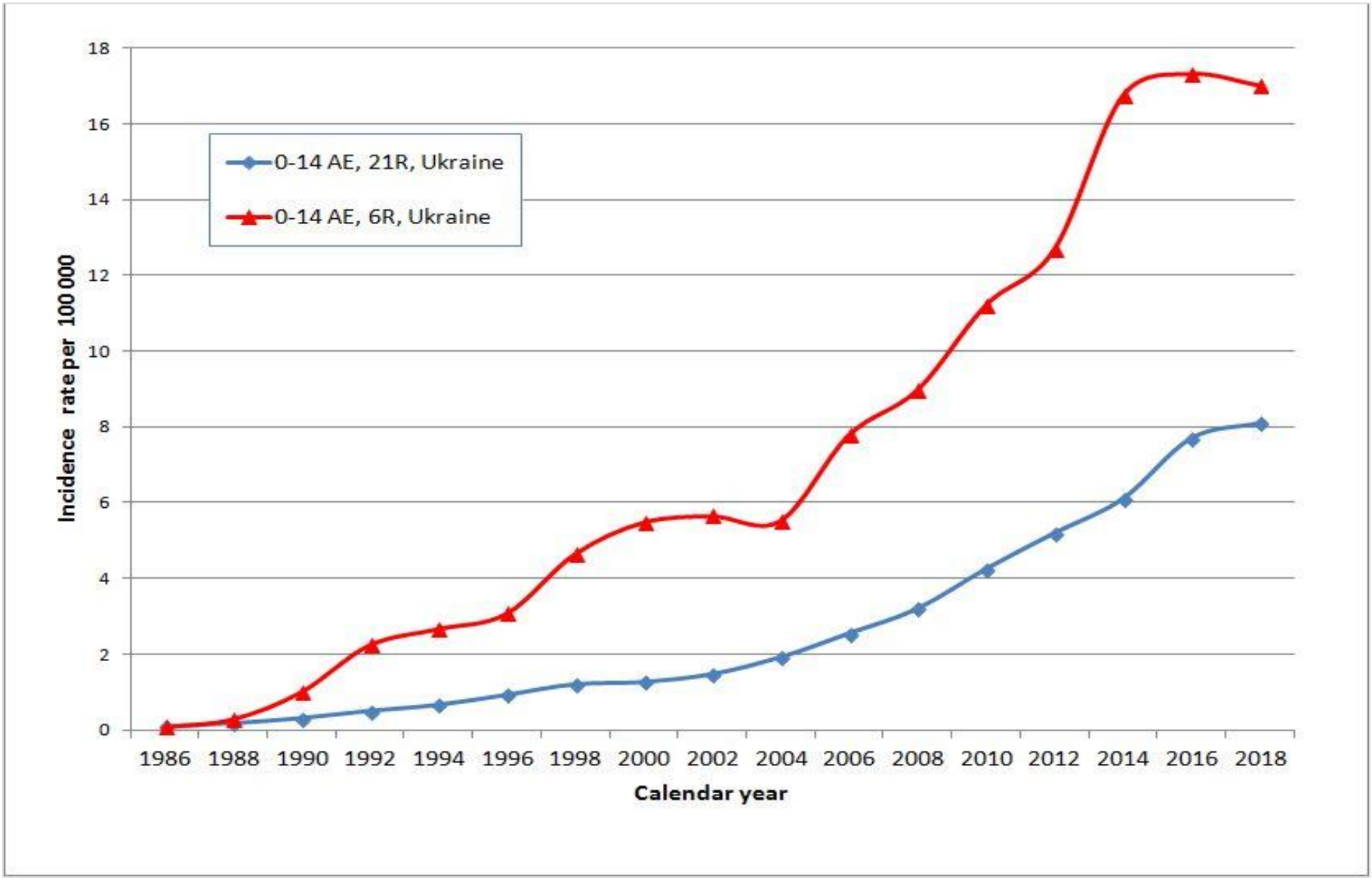
District average thyroid dose for children and adolescents aged 0-18 at the time of the Chornobyl accident



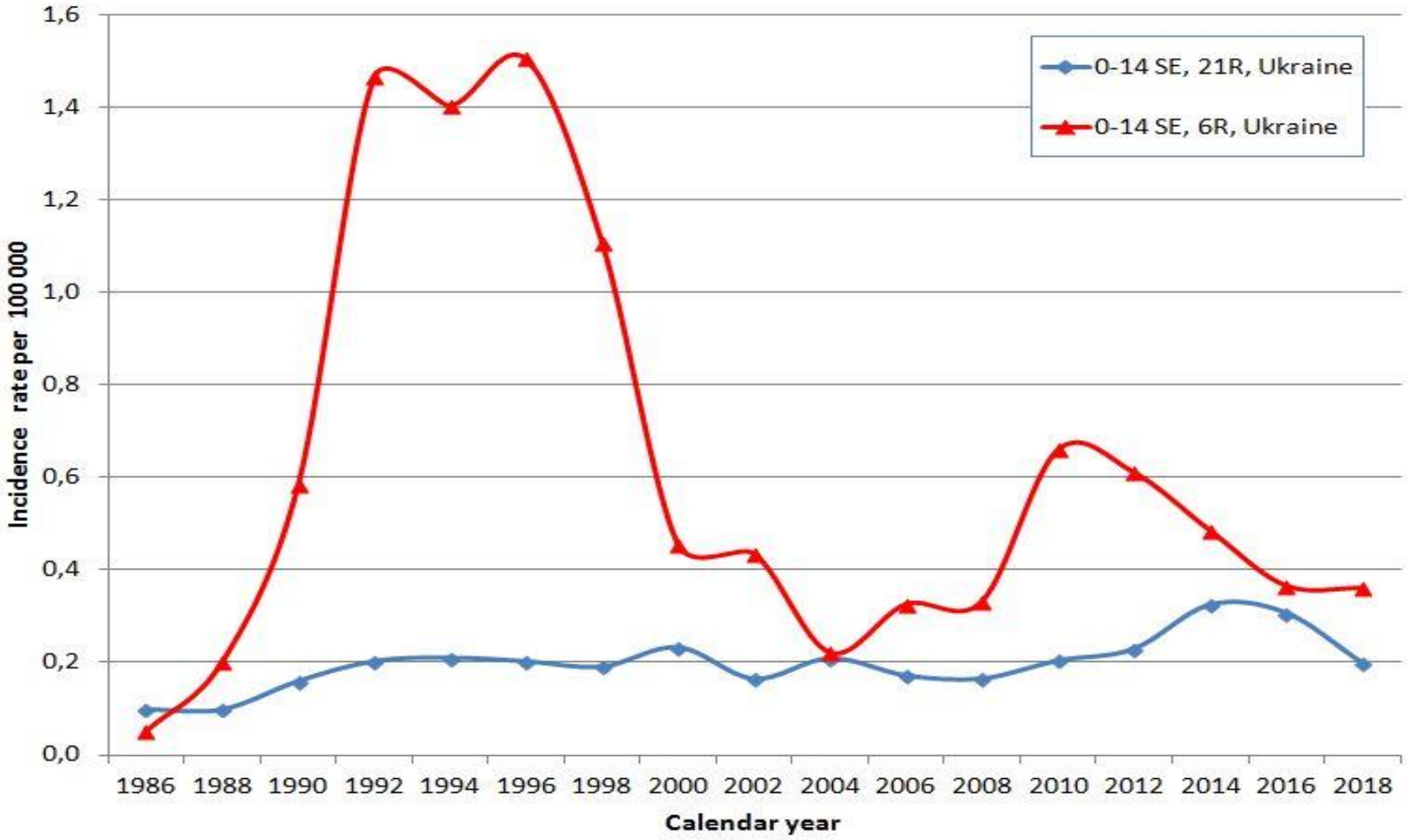
System of population-based, clinic and research registries for thyroid cancer monitoring in Ukraine



Time trends of thyroid cancer incidence in 6 and 21 regions of Ukraine for the cohort aged 0-14 years at the exposure



Time trends of thyroid cancer incidence in 6 and 21 regions of Ukraine for the cohort aged 0-14 years at the time of diagnosis



Ukrainian-American Thyroid Project

Dr. Gilbert Wheeler Beebe

Dr. Elaine Ron

Dr. Geoffrey R. Howe

RADIATION RESEARCH 161, 481–492 (2004)
0033-7587/04 $15.00

A Cohort Study of Thyroid Cancer and Other Thyroid Diseases after the Chornobyl Accident: Objectives, Design and Methods

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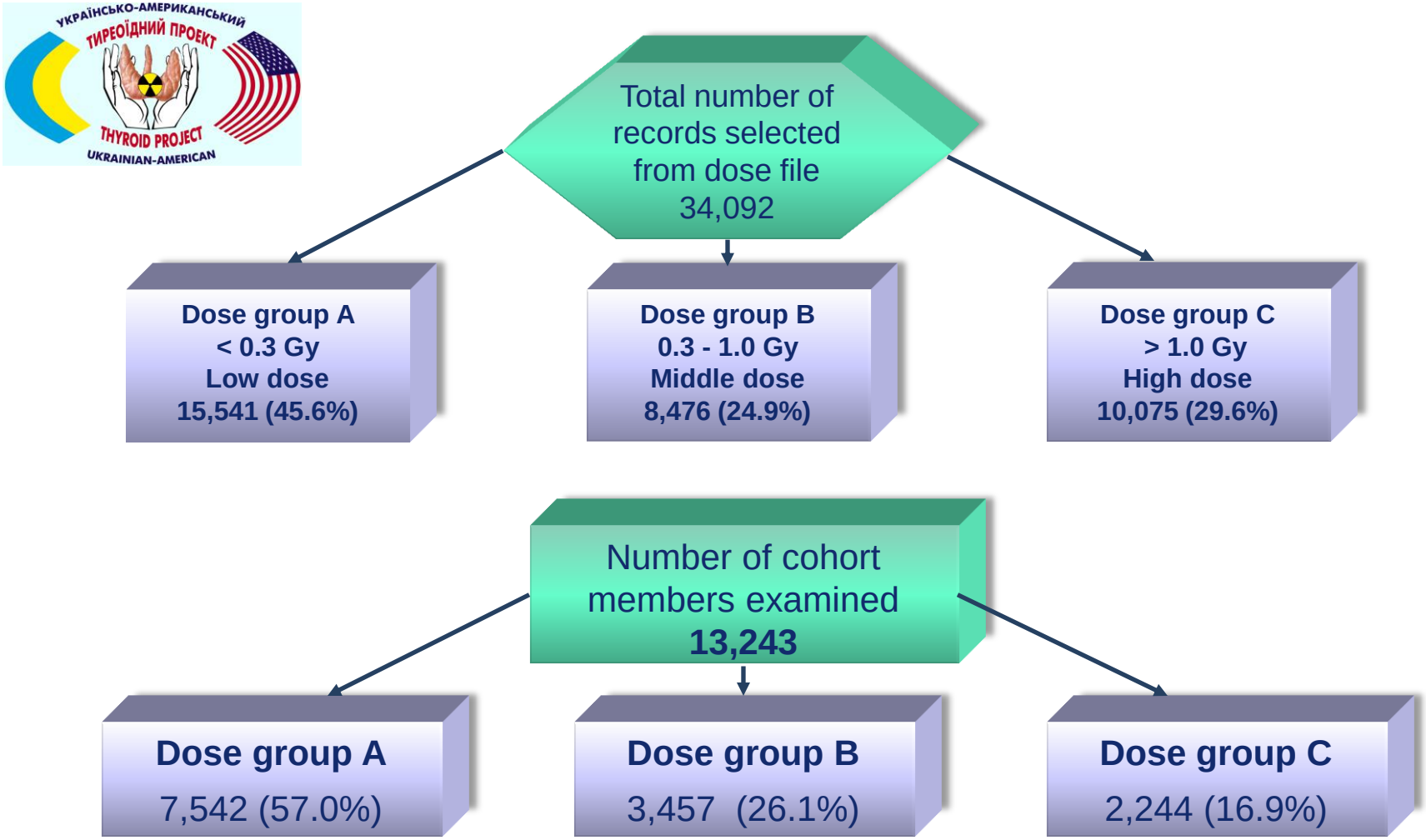
Chornobyl Thyroid Diseases Study Group of Belarus, Ukraine, and the USA. A Cohort Study of Thyroid Cancer and Other Thyroid Diseases after the Chornobyl Accident: Objectives, Design and Methods. *Radiat. Res.* 161, 481–492 (2004).

INTRODUCTION

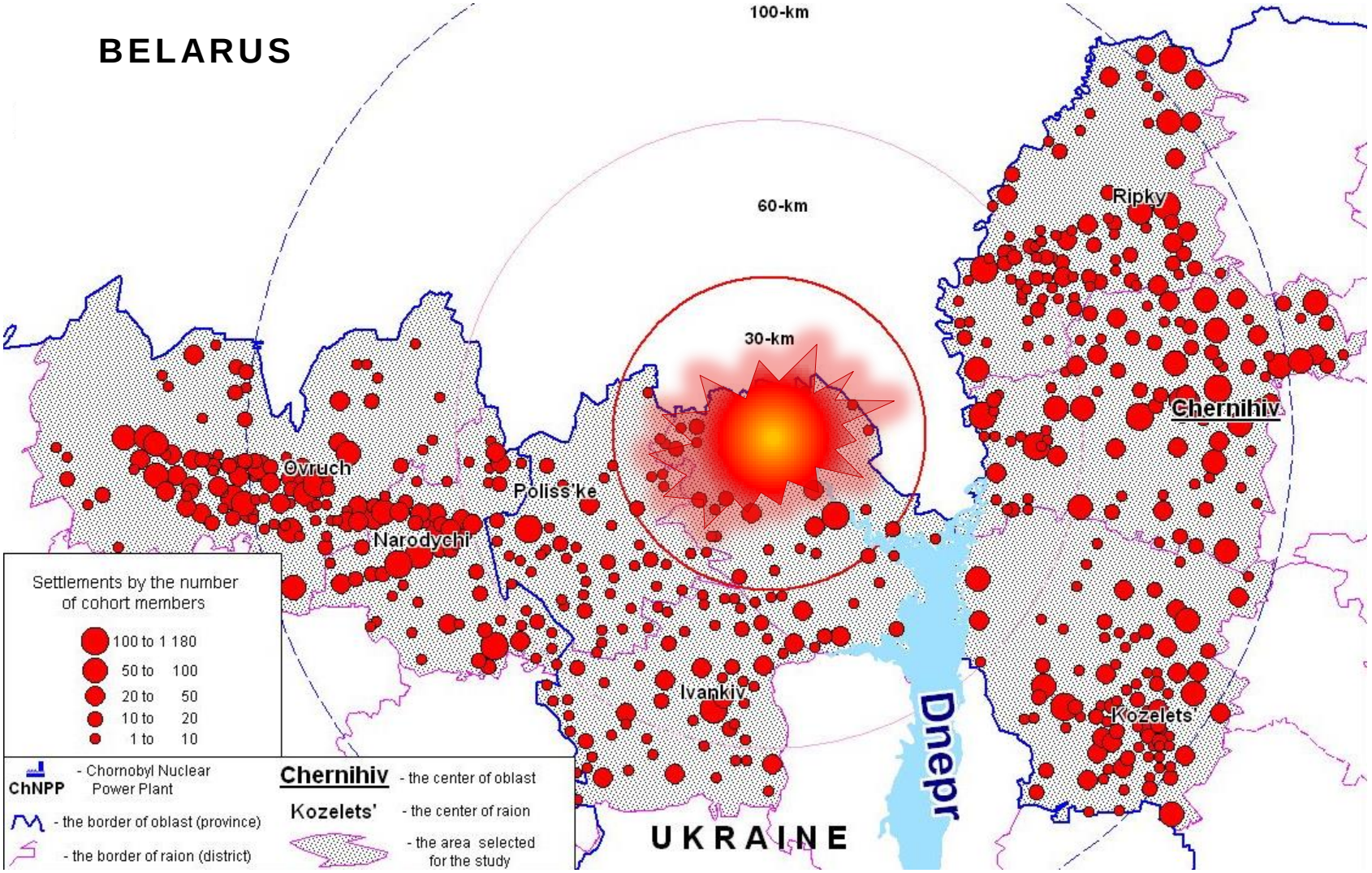
A number of epidemiological studies have shown that exposure to external X and γ radiation is associated with an increased incidence of thyroid cancer. The radiation-associated risk increases approximately linearly with dose, and the magnitude of increase is modified by age at ex-

UkrAm cohort thyroid study designed as a classical prospective cohort study of radiation risk of thyroid cancer and other thyroid pathology in Ukrainian children and adolescents exposed due to Chornobyl accident and having direct thyroid activity measurements in May-June 1986.

Distribution of selected and examined cohort members according to preliminary dose estimates



Distribution of cohort members according to the place of residence in 1986



Epidemiologic summary I-V screening cycles

1) There were five screening cycles of the UkrAm cohort between 1998-2015. The response rate in the 5th cycle was 76.3% of the original cohort or > 79% among cohort members who were alive before the 5th screening.

2) Overall compliance with recommended FNA and thyroid surgery was 92% and 89%, respectively.

3) A total of 286 UkrAm cohort members underwent thyroid surgery.

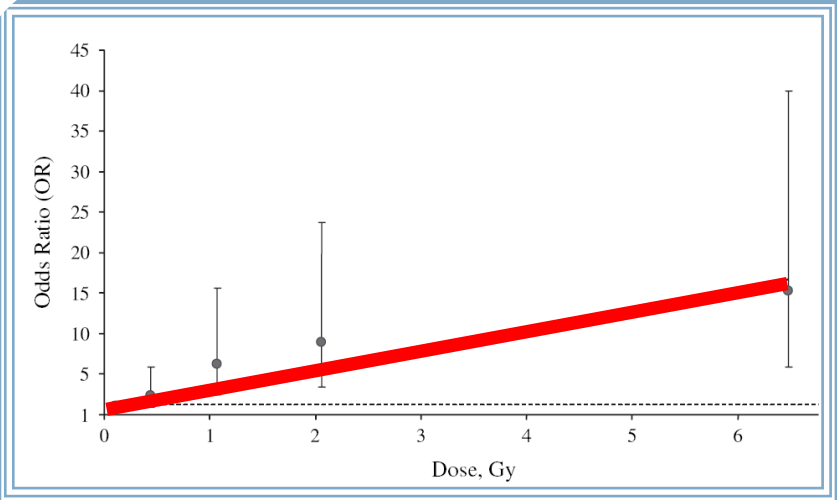
4) 14 thyroid cancers were diagnosed in 1990-1998 before the first screening.

5) 179 thyroid cancers and 89 cases of follicular adenomas (including 22 cases of combined pathology: thyroid carcinoma and follicular adenoma) were diagnosed between 1998-2015 over five screening cycles.

UkrAm: estimates of thyroid cancer risk

Prevalence: cases diagnosed in 1998-2000

Tronko M.D., Howe G.R., Bogdanova T.I. et al. JNCI, Vol. 98, 2006
Dose-response prevalence of thyroid cancers detected during first screening cycle (1998-2000)



- In the cohort 13127 screened subjects during 1998-2000 45 thyroid cancer cases were detected.
- The excess relative risk per gray (Gy) was estimated using individual doses and a linear excess relative risk model.

•Thyroid cancer showed a strong, monotonic, and approximately linear relationship with individual thyroid dose estimate (P <.001), yielding an estimated **ERR\Gy= 5.25 (95%CI = 1.70 to 27.5).** In the absence of Chernobyl radiation, 11.2 thyroid cancer cases would have been expected compared with the 45 observed.

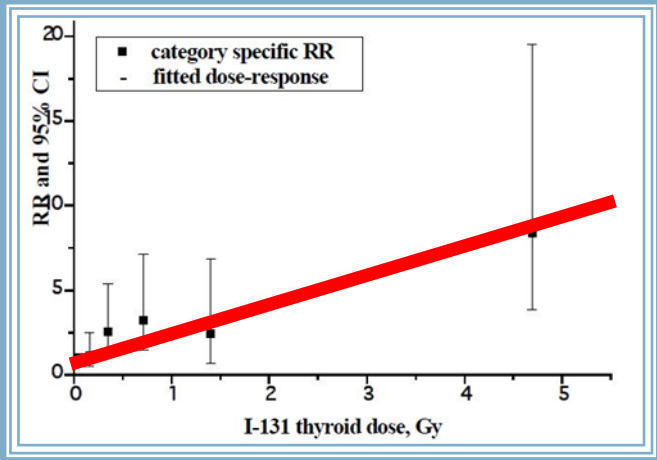
UkrAm: estimates of thyroid cancer risk

Incidence: cases diagnosed in 2001-2008

Brenner A.V., Tronko M.D., Hatch M., Bogdanova T.I. et al. EHP, March 2011, doi: 10.1289/ehp.1002674
I-131 Dose-Response for Incident Thyroid Cancers in Ukraine Related to the Chernobyl Accident

- There were 65 incident thyroid cancers diagnosed during the 2nd-4th screenings in 2001-2008 (N=12514) and about 73,000 person-years of observation.

- ERR/Gy = 1.91 (95% CI: 0.43-6.34) EAR per 10^4 PY per Gy was 2.21 (95% CI: 0.04 - 5.78).



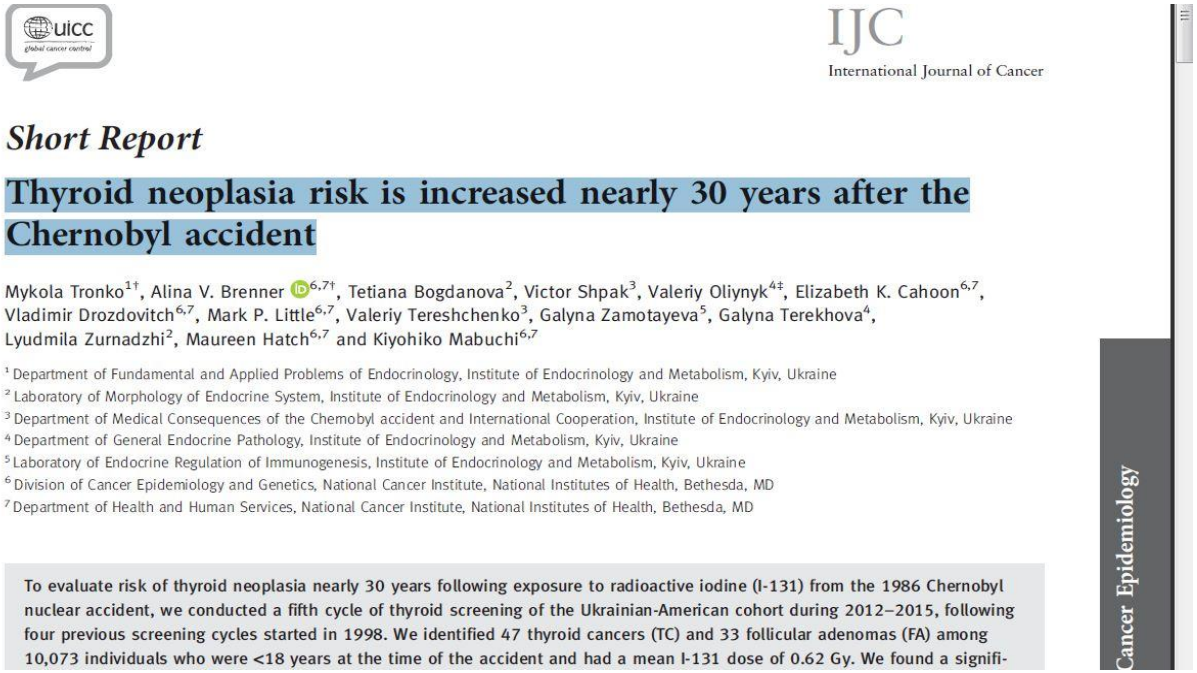
The ERR per Gy varied significantly by oblast of residence, but not by time since exposure. I-131-related thyroid cancer risks persisted for two decades following exposure.

Thyroid Cancer Risk 30 years after Chornobyl accident

Based on the fifth cycle of thyroid screening (2012–2015):

thyroid cancer EOR/Gy = 1.36 (95% CI: 0.39–4.15);
follicular adenoma EOR/Gy = 2.03 (95% CI: 0.55–6.69).

The excess risk of malignant and benign thyroid neoplasia persists nearly three decades after exposure and underscores the importance of continued follow-up of this cohort to characterize long-term pattern of I-131 risk.



UICC global cancer control

IJC
International Journal of Cancer

Short Report

Thyroid neoplasia risk is increased nearly 30 years after the Chernobyl accident

Mykola Tronko[1†], Alina V. Brenner[6,7†], Tetiana Bogdanova[2], Victor Shpak[3], Valeriy Oliynyk[4‡], Elizabeth K. Cahoon[6,7], Vladimir Drozdovitch[6,7], Mark P. Little[6,7], Valeriy Tereshchenko[3], Galyna Zamotayeva[5], Galyna Terekhova[4], Lyudmila Zurnadzhi[2], Maureen Hatch[6,7] and Kiyohiko Mabuchi[6,7]

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[2] Laboratory of Morphology of Endocrine System, Institute of Endocrinology and Metabolism, Kyiv, Ukraine
[3] Department of Medical Consequences of the Chernobyl accident and International Cooperation, Institute of Endocrinology and Metabolism, Kyiv, Ukraine
[4] Department of General Endocrine Pathology, Institute of Endocrinology and Metabolism, Kyiv, Ukraine
[5] Laboratory of Endocrine Regulation of Immunogenesis, Institute of Endocrinology and Metabolism, Kyiv, Ukraine
[6] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD
[7] Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD

To evaluate risk of thyroid neoplasia nearly 30 years following exposure to radioactive iodine (I-131) from the 1986 Chernobyl nuclear accident, we conducted a fifth cycle of thyroid screening of the Ukrainian-American cohort during 2012–2015, following four previous screening cycles started in 1998. We identified 47 thyroid cancers (TC) and 33 follicular adenomas (FA) among 10,073 individuals who were <18 years at the time of the accident and had a mean I-131 dose of 0.62 Gy. We found a signifi-

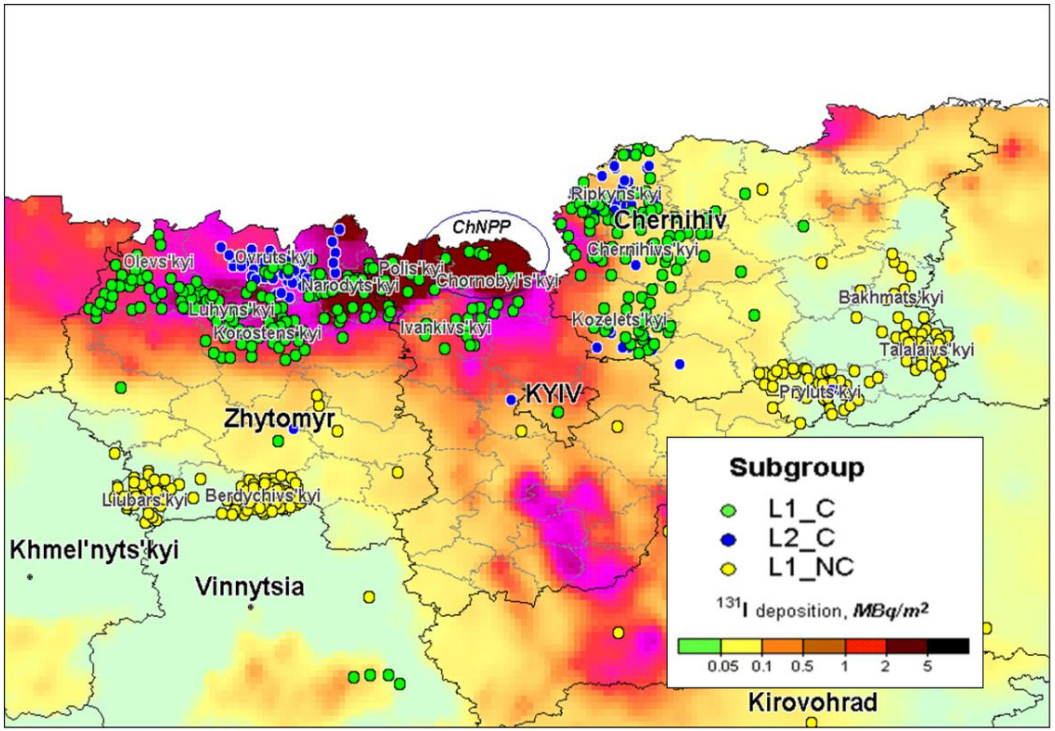
Cancer Epidemiology

(Tronko et al., IJC, 2017)

Thyroid cancer risk in the UkrAm cohort: preliminary conclusions

There is a linear dose-response between I-131 exposure and risk of thyroid cancer
The risk is significantly elevated about 30 years after the accident and may persist longer
UkrAm estimates of ERR/Gy are consistent with estimates from other Chernobyl studies as well as risks from external radiation exposure during childhood
The highest risk is observed for those irradiated at the youngest age
The ERR/Gy does not significantly vary by sex
It is important to carefully analyze the modifying effects of other factors on I-131 risk of thyroid cancer in the UkrAm cohort

Ukrainian-American in Utero Study



Residence of the UkrAm In utero cohort members in 1986

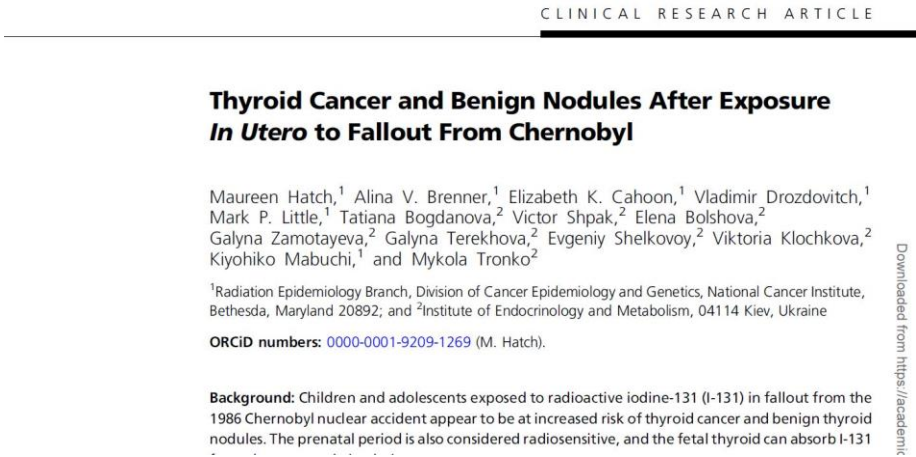
- **2,587 mother-child pairs: women pregnant on April 26,1986 or the two following months when fallout was present**
  - **1,498 from contaminated areas (individual thyroid doses are between** 0-3.23 Gy**)**
  - **1,089 from no/low-contaminated areas (individual thyroid doses are between** 0-0.37 Gy**)**

(Hatch et al., JCEM, 2009; Likhtarev et al., Health Phys, 2011)

Risk analysis of UkrAm in utero study

- **Based on 8 cases was found a markedly elevated, but not statistically significant, dose-related risk of thyroid cancer from *in utero* exposure to I-131: EOR/Gy=3.91 (95%CI: -1.49;65.7) .**
- **There was a strong and significant association between I-131 thyroid dose and screen-detected large benign nodules (>=10 mm): (EOR/Gy = 4.19, 95% CI: 0.68, 11.62; P = 0.009) but no significant increase in risk for small nodules (<10 mm)**

(Hatch et al., JCEM, 2019)



CLINICAL RESEARCH ARTICLE

Thyroid Cancer and Benign Nodules After Exposure *In Utero* to Fallout From Chernobyl

Maureen Hatch,[1] Alina V. Brenner,[1] Elizabeth K. Cahoon,[1] Vladimir Drozdovitch,[1] Mark P. Little,[1] Tatiana Bogdanova,[2] Victor Shpak,[2] Elena Bolshova,[2] Galyna Zamotayeva,[2] Galyna Terekhova,[2] Evgeniy Shelkovoy,[2] Viktoria Klochkova,[2] Kiyohiko Mabuchi,[1] and Mykola Tronko[2]

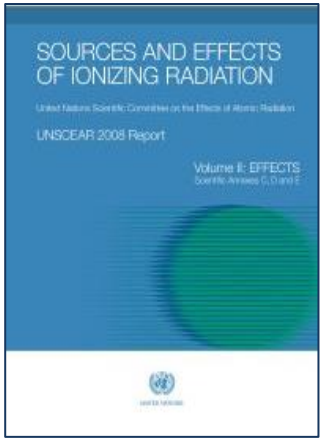
[1]Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland 20892; and [2]Institute of Endocrinology and Metabolism, 04114 Kiev, Ukraine

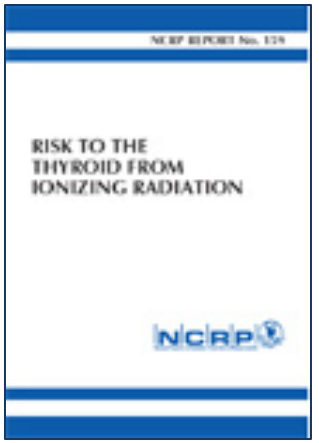
ORCiD numbers: 0000-0001-9209-1269 (M. Hatch).

Background: Children and adolescents exposed to radioactive iodine-131 (I-131) in fallout from the 1986 Chernobyl nuclear accident appear to be at increased risk of thyroid cancer and benign thyroid nodules. The prenatal period is also considered radiosensitive, and the fetal thyroid can absorb I-131

Evaluation of the scientific results and the research potential of the UkrAm cohort by the international experts

UNSCEAR 2008 Report: ***"Sources and effects of ionizing radiation".***
Volume II. Annex D - Health effects due to radiation from the Chernobyl accident

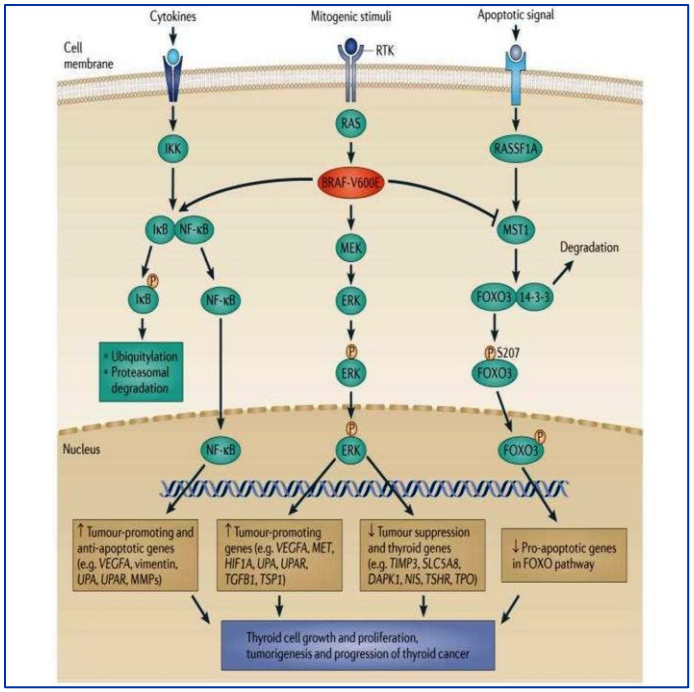




NCRP Report No. 159, Risk to the Thyroid from Ionizing Radiation, Bethesda (MD), 2008

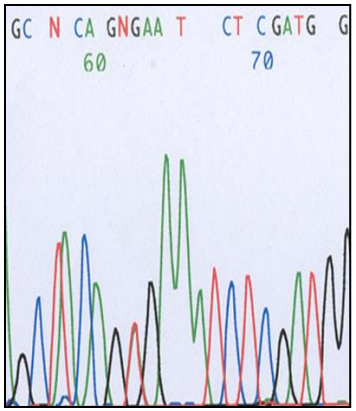
EC Project ARCH (Agenda for Research on Chernobyl Health (http://arch.iarc.fr/)) Williams et al., J Radiol Prot, 2011

Based on UkrAm and BelAm thyroid cohorts there was recommended to create the Chornobyl Life Span Cohort



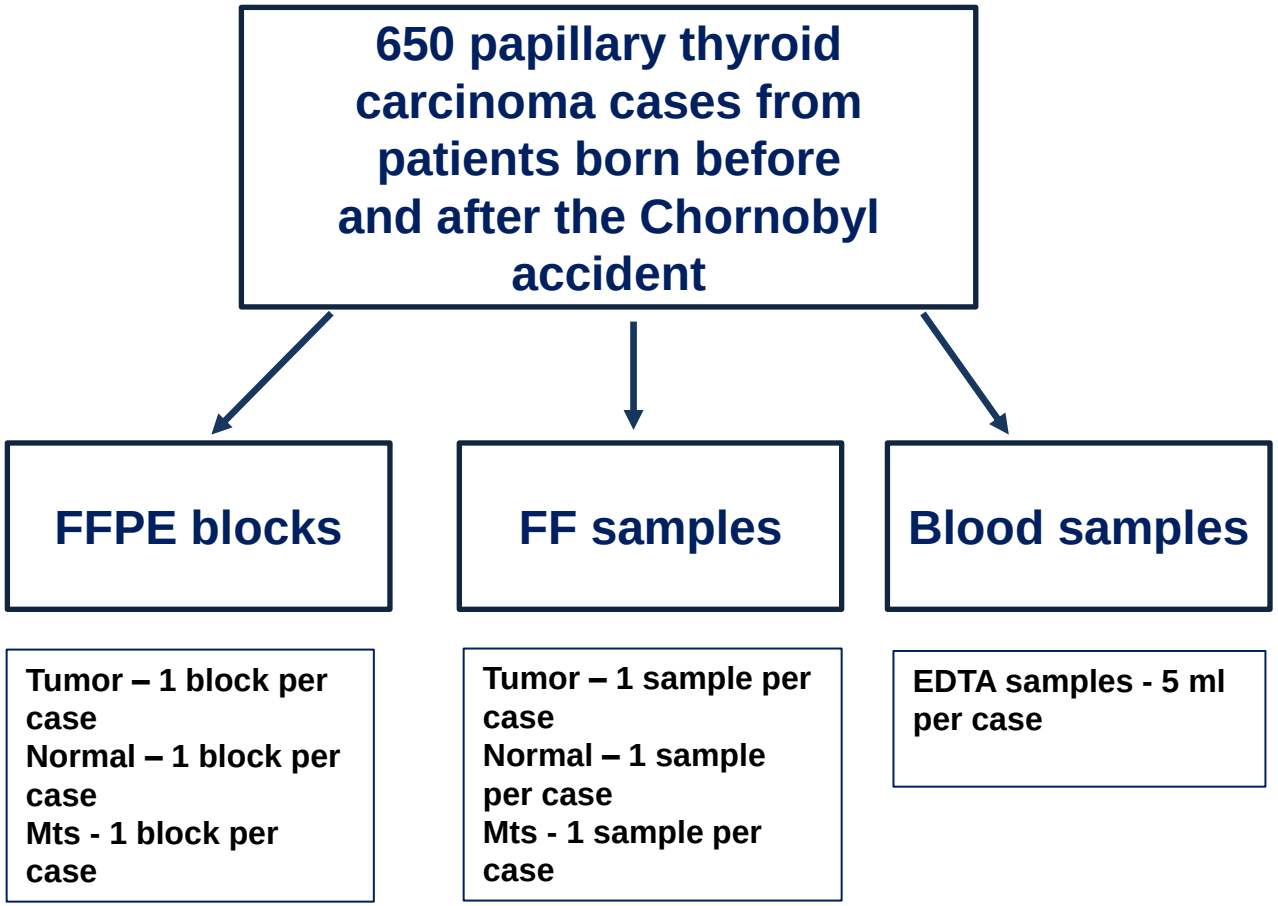
The main factors in the development of papillary thyroid carcinoma are changes in the MAP-kinase signaling pathway. This pathway activates various gene alterations:
different gene fusions
(most often *RET-PTC* translocations)
or point mutations
(most often the *BRAF* ^{V600E} mutation)

BRAF ^{V600E}
mutation



Expression of mutated V600E BRAF protein

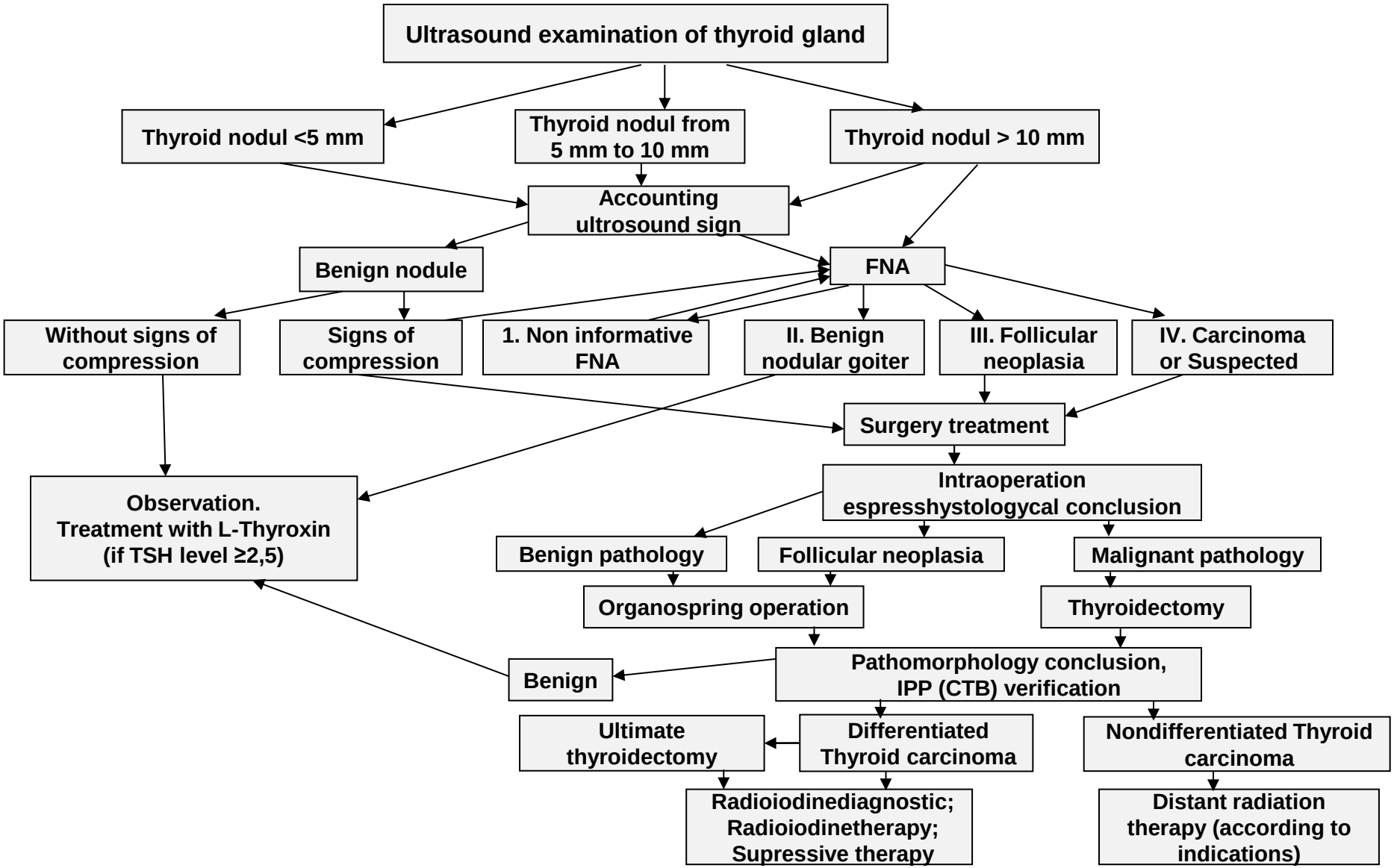
Comprehensive Genomic Characterization of Radiation-Related Thyroid Cancer (NCI, IEM, CTB)

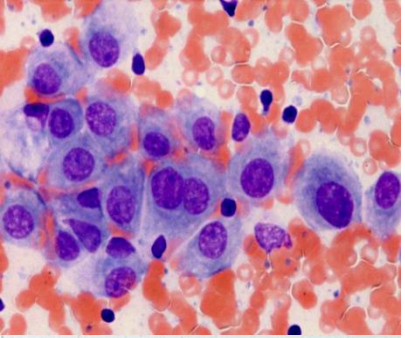


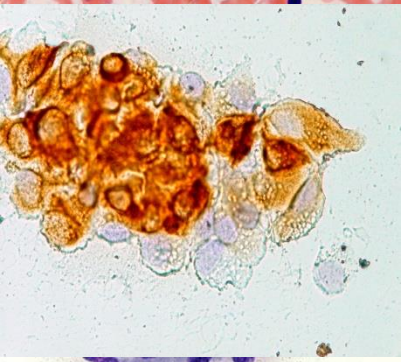
- **Institute of Endocrinology today has a complete cycle of diagnosis and treatment of nodular thyroid pathology and well differentiated thyroid cancer**

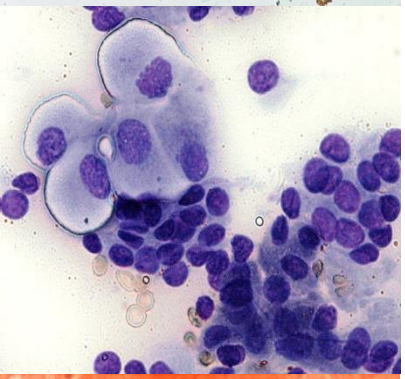
- **Conducting clinical screening studies in the cohort of the Ukrain-American project allowed to create a modern unified clinical protocol of diagnosis, personalized treatment and long-term observation of persons with nodular thyroid pathology**

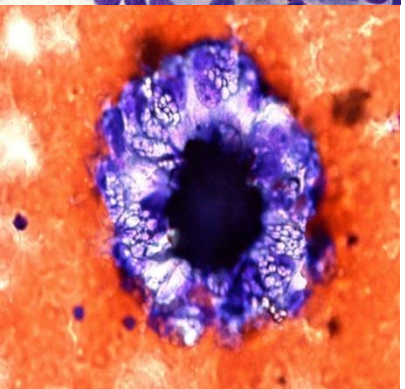
Actual clinical protocol for patients with thyroid nodules SI "V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine"











About 98 % of patients with differentiated thyroid cancer have 20-year survival due to the use of radioiodine therapy.

However, the problem of diagnosis and treatment of thyroid cancer is radioiodine-resistant metastases that occur in 4-20 % of cases and for which radioiodine therapy becomes impossible. Patients with radioiodine-resistant metastases have reduced median survival.

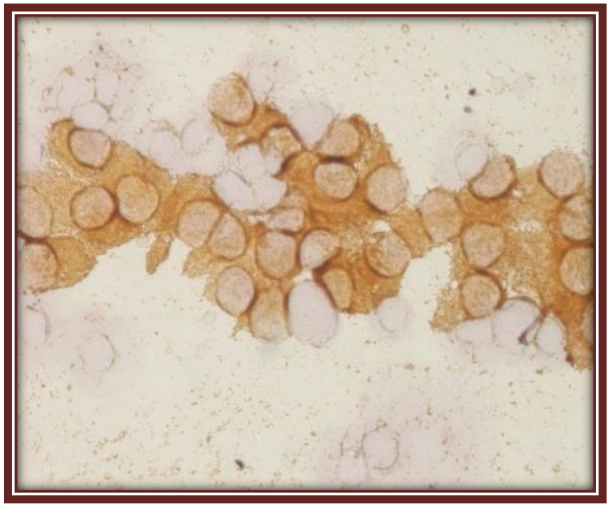
Methods of early preoperative forecasting of radioiodine-resistant of papillary thyroid cancer were developed using the preoperative cytological markers.

For the first time, cytological methods of monitoring of radioiodine-resistant metastases are developed, with the help of their FNA biopsy, determination in the expression of thyroid peroxidase and thyroglobulin, to assess the ability of metastasis to accumulate radioiodine and the effectiveness of radioiodine therapy. If the expression of thyroid peroxidase is absent, there is the necessary surgical removal of metastasis. If the expression of thyroglobulin is less than 85%, radioiodine-resistance of the metastasis is predicted.

Prediction of radioiodine-resistance
Papillary carcinoma

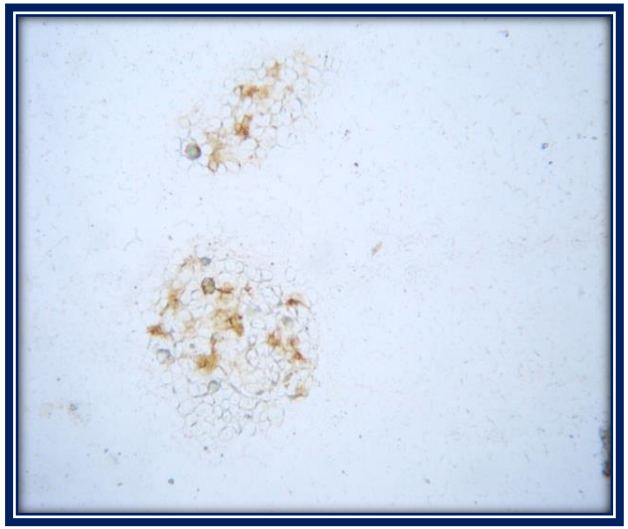
Immunocytochemicals preoperative markers of radioiodine-resistance of papillary thyroid cancer

Thyroid peroxidase



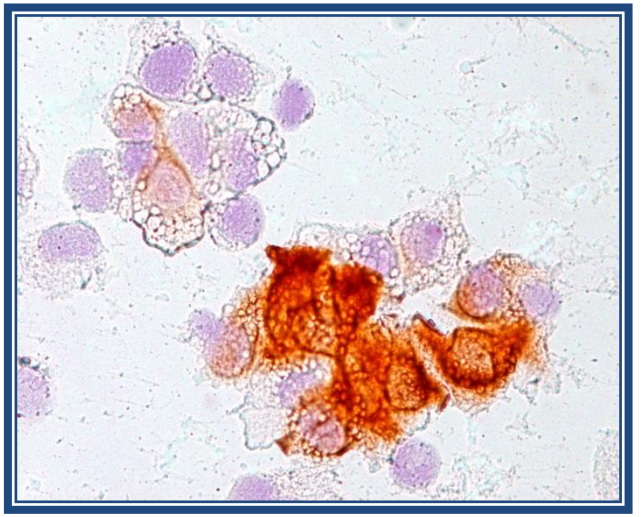
0-15 % - radioiodine-resistance

Thyreoglobuline



< 85 % - radioiodine-resistance

Cytoceratin 17



> 10 % - radioiodine-resistance

Perspective research directions (Thyroid Cancer), I

- **Monitoring of time trends of thyroid cancer for high risk population groups and whole Ukraine.**
- **Development of a advanced methodology for assessing individual and population average thyroid doses**
- **Comprehensive dose-response model for children and adolescents**
- **Statistically significant risk estimations for the children exposed in prenatal and early postnatal age**
- **Dose–risk relationship by tumor type**

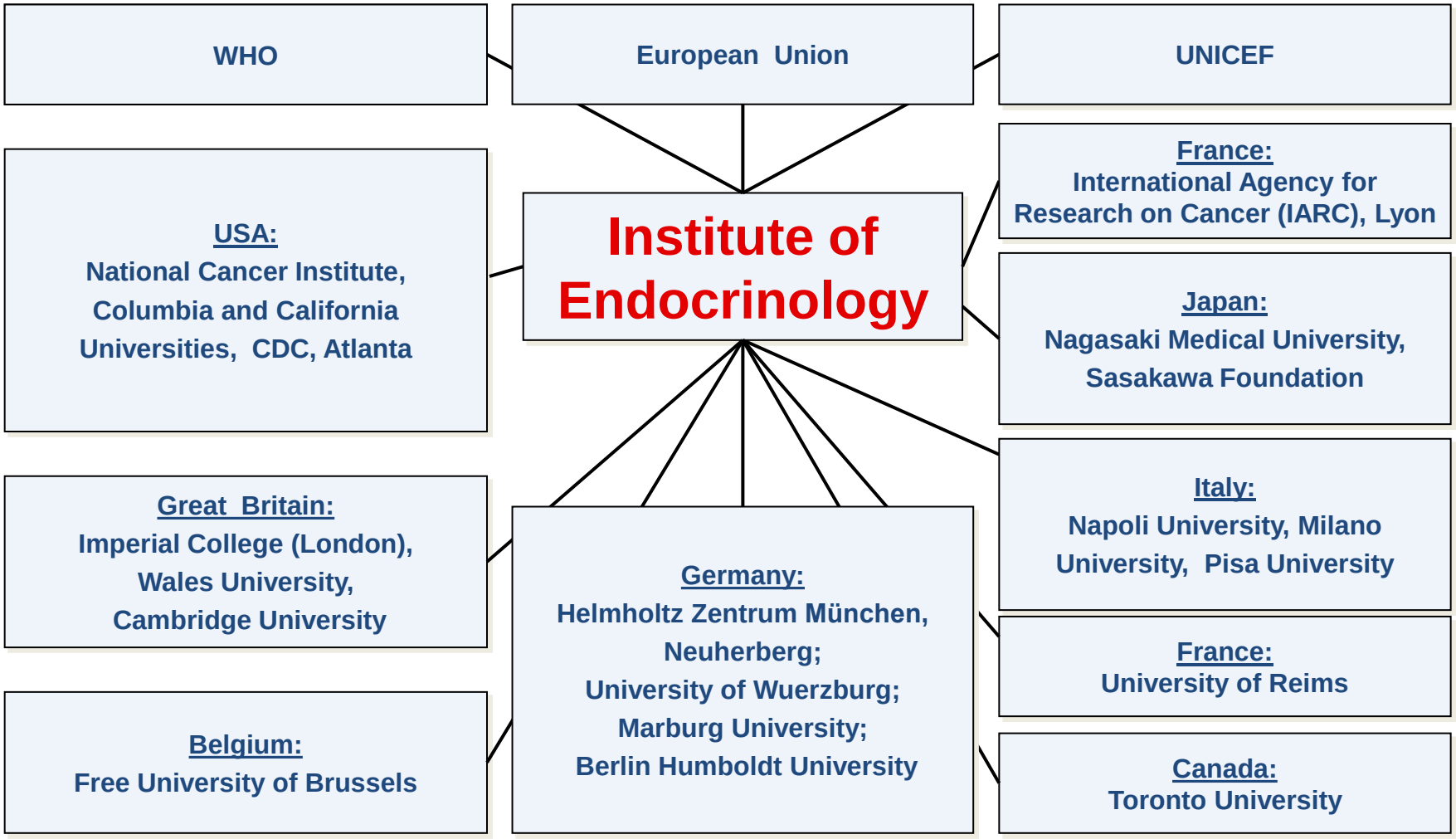
Perspective research directions (Thyroid Cancer), II

- Potential interaction with, or effect modification by, other risk factors
- The lifetime risk of radiation-induced thyroid cancer
- Creation of mechanistic (biologically based) radiation risk models
- Identification of biomarkers for radiation-induced thyroid cancer
- Morphologic features of radiation-induced thyroid tumors
- Genome-wide association studies of radiation-induced thyroid carcinomas

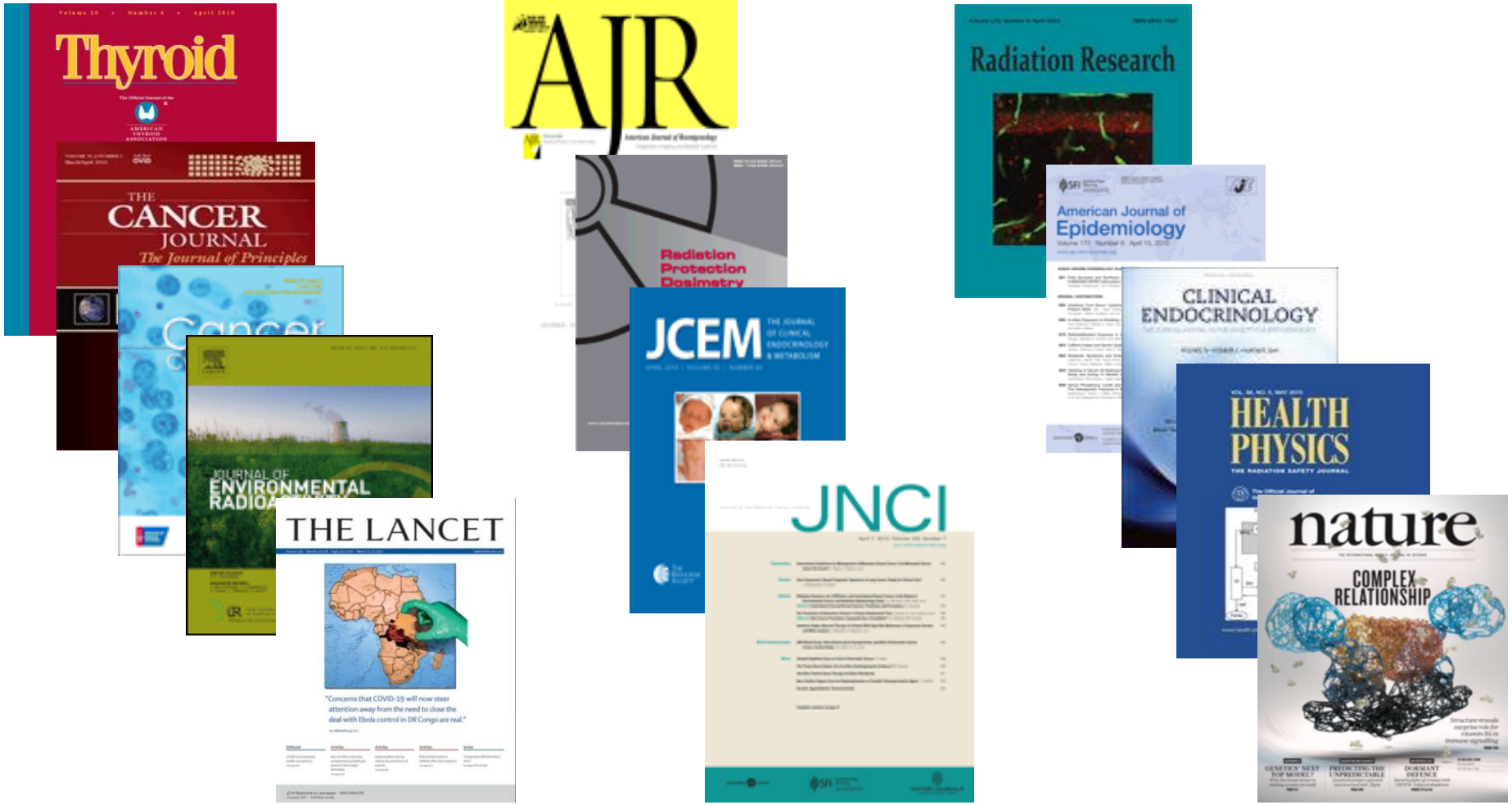
Perspective research directions (other thyroid and nonthyroid pathology), III

- Radiation risk of thyroid nodules
- Functional thyroid disorders
- Pathology of the parathyroid gland
- Risk of nonthyroid oncopathology among the UkrAm cohort members
- Breast cancer risk among the UkrAm cohort members and their mothers
- Risk of radiation-induced second primary malignancy after radioiodine treatment of differentiated thyroid cancer
- Reproductive function after exposure in early life or prenatally

Cooperation of Institute of Endocrinology with international organizations and leading research institutions



Scientific results published in leading National and International peer-reviewed Journals




THANK YOU
FOR YOUR
ATTENTION!