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AGE AND GENDER PATTERNS OF THYROID CANCER INCIDENCE IN UKRAINE DEPENDING ON THYROID RADIATION DOSES FROM RADIOACTIVE IODINE EXPOSURE AFTER THE CHORNOBYL NPP ACCIDENT

The objective of this study was to investigate the thyroid cancer incidence in a whole territory of Ukraine and to clear up its age and gender patterns depending on average regional (oblast) thyroid doses from radioactive iodine due to the Chornobyl accident.

Materials and methods. On the basis of average accumulated thyroid doses from radioactive iodine the geographical regions of Ukraine with low and high average thyroid doses were identified for a comparative analysis performance. Methods of descriptive epidemiology were used.

Results. The level and dynamics of thyroid cancer incidence were analyzed in different gender and age groups (both for attained age and age at the moment of the Chornobyl accident). Results of this study confirmed the radiation excess of thyroid cancer in individuals who were children and adolescents in 1986. Some excess was observed in elder age groups too. Especial situation was observed in female age group 40–49 at the moment of the Chornobyl accident i.e. the age-specific thyroid cancer incidence rates were significantly higher in "high exposure" regions comparing with "low exposure" ones during all years of observation within 1989–2009.

Conclusions. A probable radiation excess of thyroid cancer was suggested not only in children and adolescents but also in adult age groups. In elder age groups this excess was less expressed and manifested after a longer period of time. The origin of the phenomenon in female age group of 40–49 is unclear now. Hypothesis of combined effect of radiation and natural changing of hormonal status in this age should be checked in the future studies.

Key words: thyroid cancer, malignant tumors, incidence, Chornobyl accident, radioactive iodine.

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Вікові та гендерні особливості захворюваності на рак щитоподібної залози в Україні залежно від доз опромінення щитоподібної залози радіоактивним йодом внаслідок аварії на ЧАЕС

Метою цього дослідження було вивчити захворюваність на рак щитоподібної залози на всій території України та виявити статеві та вікові особливості залежно від середньообласних доз на щитоподібну залозу від радіоактивного йоду внаслідок аварії на ЧАЕС.

Матеріали та методи. На основі середніх накопичених щитоподібною залозою доз опромінення радіоактивним йодом географічні регіони України для проведення порівняльного аналізу було поділено на дві групи - з "високими" та "низькими" дозами. В дослідженні використовувались методи дескриптивної епідеміології.

Результати. Проаналізовано рівень та динаміку захворюваності на рак щитоподібної залози в різних статево-вікових групах (відносно як віку на момент діагнозу, так і під час аварії на ЧАЕС). Підтверджено радіаційний ексцес у осіб, які були дітьми та підлітками на момент аварії. Певний ексцес спостерігався і в старіших вікових групах. Особлива ситуація мала місце у жінок віком 40–49 років на момент аварії, серед яких повікові показники захворюваності на територіях з "високими" дозами були достовірно вищими упродовж всього періоду спостереження 1989–2009 рр.

Висновки. Окрім дитячих та підліткових груп, результати дослідження свідчать про вірогідний радіаційний ексцес у дорослих. У старіших вікових групах цей ексцес менш виражений та проявляється після більш тривалого часу. Походження згаданого феномену у жінок віком 40–49 років на момент аварії поки що залишається неясним. У подальших дослідженнях слід перевірити гіпотезу комбінованого впливу радіації та природних змін гормонального стану у цьому віці.

Ключові слова: рак щитоподібної залози, злоякісні новоутворення, захворюваність, аварія на ЧАЕС, радіоактивний йод.

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INTRODUCTION

Chornobyl accident caused the exposure of thyroid in large groups of inhabitants of Ukraine, Russia and Belarus at the account of incorporated ^{131}I on thyroid [1]. The increase of thyroid cancer incidence is one of the most considerable health consequences of the Chornobyl accident in territories of Ukraine, Belarus and Russia surrounding the Chornobyl Nuclear Power Plant. First radiation-induced thyroid cancer cases were registered four years after the Chornobyl accident [2–5]. It is also remarkable that Chornobyl accident is a topic of attention in quite remote countries and it leads to research of its possible consequences in population of these countries [6–12].

At present quite many papers already are dedicated to estimation of thyroid cancer risk in people exposed in childhood and adolescence to radioactive iodine after the Chornobyl accident [13–21]. In all these studies a significant radiation risk is found and radiation origin of thyroid cancer excess in these age groups after the Chornobyl accident is of no doubts.

Adult population drew less attention here and study results in thyroid cancer incidence in adults regarding the Chornobyl accident are quite controversial and not enough clear. There are three distinct most affected groups being an object of research interest: the recovery opera-

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tion workers, evacuees, and residents of the most heavily contaminated territories. In all these three groups an excess of thyroid cancer incidence was registered (comparing with the national level), but its radiation origin is disputable because of a potential influence of screening and implementation of modern ultrasound diagnostic equipment to the registered thyroid cancer cases [16, 22–24]. In Russia a significant radiation excess of thyroid cancer was found only in age groups of affected population been exposed in childhood [16]. Authors explain an increase of frequency of this disease in elder age groups by the non-radiation factors. I. Likhtarev et al. [25] suggest that screening-effect is the only reason of increase of the registered thyroid cancer incidence rate in adults.

On the other hand M. Malko [26] concludes that the 692 radiation-induced thyroid cancer cases were realized in children and 3709 ones in adults during 1997–2000 in Belarus. Another study [27] that covered all territory of Belarus showed more dramatic increase of thyroid cancer incidence in the most contaminated Gomel and Mogilev regions comparing with the rest of territory of Belarus. A statistically significant excess of this disease comparing with the rest territory of Belarus was registered in these regions not only in age group 15-34 (i. e. children at the moment of the Chornobyl accident) but in elder population as well. But authors avoid making conclusion whether this excess is of radiation origin.

Therefore studies of thyroid cancer incidence in Ukraine are still actual. It should be noted that the majority of previous studies of thyroid cancer incidence were fragmentary because they covered only separate groups of population affected due to the Chornobyl accident. However in respect to the rarity of thyroid cancer the study among the entire Ukrainian population including all population groups affected due to the Chornobyl accident allows obtaining the most reliable patterns and trends.

OBJECTIVE

The objective of this study was to investigate the thyroid cancer incidence in a whole territory of Ukraine and to clear up their age and gender patterns depending on average regional (oblast) thyroid radiation doses from radioactive iodine due to the Chornobyl accident.

MATERIALS AND METHODS

This was an ecological study generalizing the population data. This study was based on the existing system of registration of malignancies and the system of population registration. Unlike the similar study performed by Tronko et al. [28] this one covers not only children and adolescents but also the adult age groups.

Data on annual number of thyroid cancer cases within 5-year age groups were obtained from annual statistical reports of National Cancer Register of Ukraine. To calculate the age-specific and age-adjusted thyroid cancer incidence rates the information about annual number of population in Ukrainian regions with distribution by sex and 5-years age groups was collected. Sources of these data were:

➢ values of the All-Union Census of 1989 and All-Ukrainian Census of 2001;
➢ official publications of the State Committee of Statistics in 1989–2010;
➢ annual state statistical reports of regional authorities of statistics.

Data published in the National Report of Ukraine (2011) were used [29] to evaluate a possible role of radiation in forming of thyroid cancer incidence rate. These data contain average thyroid doses in all regions of Ukraine. On the basis on these data all regions of Ukraine were separated into two groups i.e. “high exposure” and “low exposure” areas (Fig. 1).

Cherkasy, Chernihiv, Kyiv, Rivne, Zhytomyr regions were designated as “high exposure” areas (they are situated close to Chornobyl). As is seen the values of average thyroid doses for these regions were much higher than for the rest ones. Conditional boarding value between these groups was defined as 35 mGy. Kyiv city is included in the first group also despite its mean of average thyroid dose is only 32 mGy (but higher than in all other territories). It is reasoned by the fact that significant part of population evacuated from the 30 km zone now resides just in Kyiv. The population of the rest regions (“low exposure”) was signed as a control.

Methods of descriptive epidemiology were used [30] for data analysis. Annual age-specific and age-standardized incidence rates (adjusted using the World standard population) were calculated. To examine the statistical significance of difference between the two rates the “rate ratio” (RR) indexes were calculated with 95 % confidence interval (95 % CI) on the basis of presupposition that Poisson distribution is correct in this case. Approximation proposed by Smith [31] was used in our work here.

Figure 1. **Average accumulated thyroid doses in all regions of Ukraine according to [29]**

Age-specific and age-standardized incidence rates were calculated not only for attained age groups but for age groups at the moment of the Chornobyl accident. For instance the age group 0–4 at the moment of the Chornobyl accident was 5–9 years old of attained age in 1991 or 10–14 in 1996. In years between 1986, 1991, 1996, 2001 and 2006 the extrapolated data were used because primary data on thyroid cancer cases number and number of the population were available only in five-year age groups (0–4, 5–9 etc.).

Extrapolation was performed by the following way:

$$\sum a_{k}^{i+n} = \sum \left(\frac{n}{5}\cdot a_{k}^{i} + \frac{5-n}{5}\cdot a_{k+1}^{i}\right),$$

where *a* is a number of thyroid cancer cases in a population in *k* age group and in (*i*+*n*) year. Value of *i* is a year among 1986, 1991, 1996, 2001 and 2006 (i.e. difference between those and 1986 is multiple of 5) for the year of calculation; *n* is a difference between the last "multiple" and calculated years.

Age-specific incidence rates are presented for 10-years age groups both for attained age and age at the moment of Chornobyl accident.

RESULTS

Thyroid cancer incidence rate and its dynamics were quite different in population of these two groups of regions. The level and average annual increment of thyroid cancer incidence were much higher in the “high exposure” regions both in males and females (Fig. 2).

During the study period (1989-2009) the age-standardized thyroid cancer incidence rate in female population of “high exposure” regions increased from 3.34 to 9.81 per 100 thousand i.e. in 2.9 times. Meanwhile in females living in "low exposure" regions the mentioned rates were 2.51 and 5.19 i.e. there was a 2.1-fold increase.

In males at the start of observation (1989) the thyroid cancer incidence rates were similar in both groups of areas – 0.87 per 100 thousand. In 2009 it increased to 2.30 in "high exposure" and to 1.42 in “low exposure” regions, i.e. in 2.6 and 1.6 times respectively. Comparison of trends suggests a statistically significant difference ($P<0.01$) between regression coefficients. In “high exposure” areas the thyroid cancer incidence rates increased much

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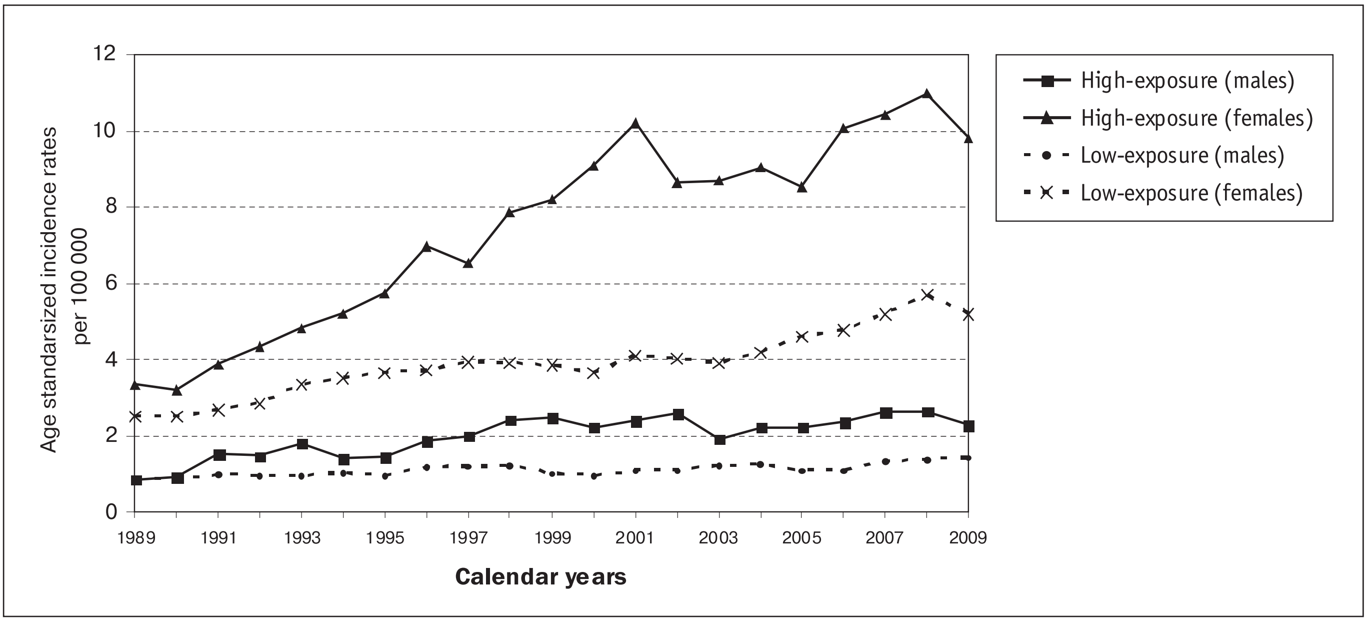

Figure 2. Thyroid cancer incidence in population of Ukraine living in "high exposure" and "low exposure" regions in 1989–2009

Note. Regression coefficients b ± s.e(b): "High exposure" (males) 0.073 ± 0.011; "low exposure" (males) 0.021 ± 0.004; "high exposure" (females) 0.382 ± 0.029; "low exposure" (females) 0.132 ± 0.010

faster both in males and females during the period of observation.

Because of very different vulnerability of thyroid gland to ionizing radiation in specific age groups and comparatively short-time exposure from the ^{131}I (the main source of thyroid irradiation) it is reasonable to compare the age-specific incidence rates just basing on age at the moment of the Chornobyl accident. Such comparison of trends of thyroid cancer incidence rate between "high exposure" and "lower exposure" regions is presented in Figures 3, 4.

In age group 0–9 at the moment of the Chornobyl accident a statistically significant excess in "high exposure" territories was observed in all years since 1991 both in males and females (except only year 2004 in males). The values in age groups of 10–19, 20–29, 30–39 years old at the moment of the Chornobyl accident have similar trends but the statistically significant excess manifested after a longer time vs. youngest age group.

Very different values were observed in an age group 40–49 for males and females. Peculiarities of male subpopulation in this age group were also similar to that in younger ones but they were less expressed. A statistically significant difference between "high exposure" and "low exposure" regions was registered only in five years - less than in any younger age group.

There was another situation in females of this age group at the moment of the Chornobyl accident. As is seen in the figure the difference between age-specific thyroid cancer incidence rates was statistically significant in absolutely all years of observation within 1989–2009. This phenomenon occurred only in this gender and age group.

Along with the age-specific thyroid cancer incidence rates the trends of relative risk of this disease in territories of "high exposure" vs. the rest territory of Ukraine was evaluated in different age groups. Rate ratio is just the index of a relative risk. Changes of a rate ratio for various age and sex groups are presented in Figures 5 and 6.

As is seen in presented figures the RR peaks in youngest group 0–9 (at the moment of the Chornobyl accident) were in 1991 both in males and females. In this age group 1991 was the first year when confidence intervals indicated statistically significant excess in "high exposure" territories. This fact confirms the results of different studies the authors of which concluded the latency period of radiation induced thyroid cancer being ~5 years.

The RR trends in elder age groups were much smoother. Particularly it can be explained by higher incidence rates and less dependence of RR on each thyroid cancer case. Besides in elder age groups the values of RR were much lower than in the group 0-9 years old. In male age group 10-19 the maximal values of RR were in 1999 (3.77, 95 % CI 1.46–9.73) and in the same age group in females the maximal value was in 2000 (3.19, 95 % CI 2.04–4.98) with a following decrease.

As to the rest age groups a character of RR dynamics had some differences between males and

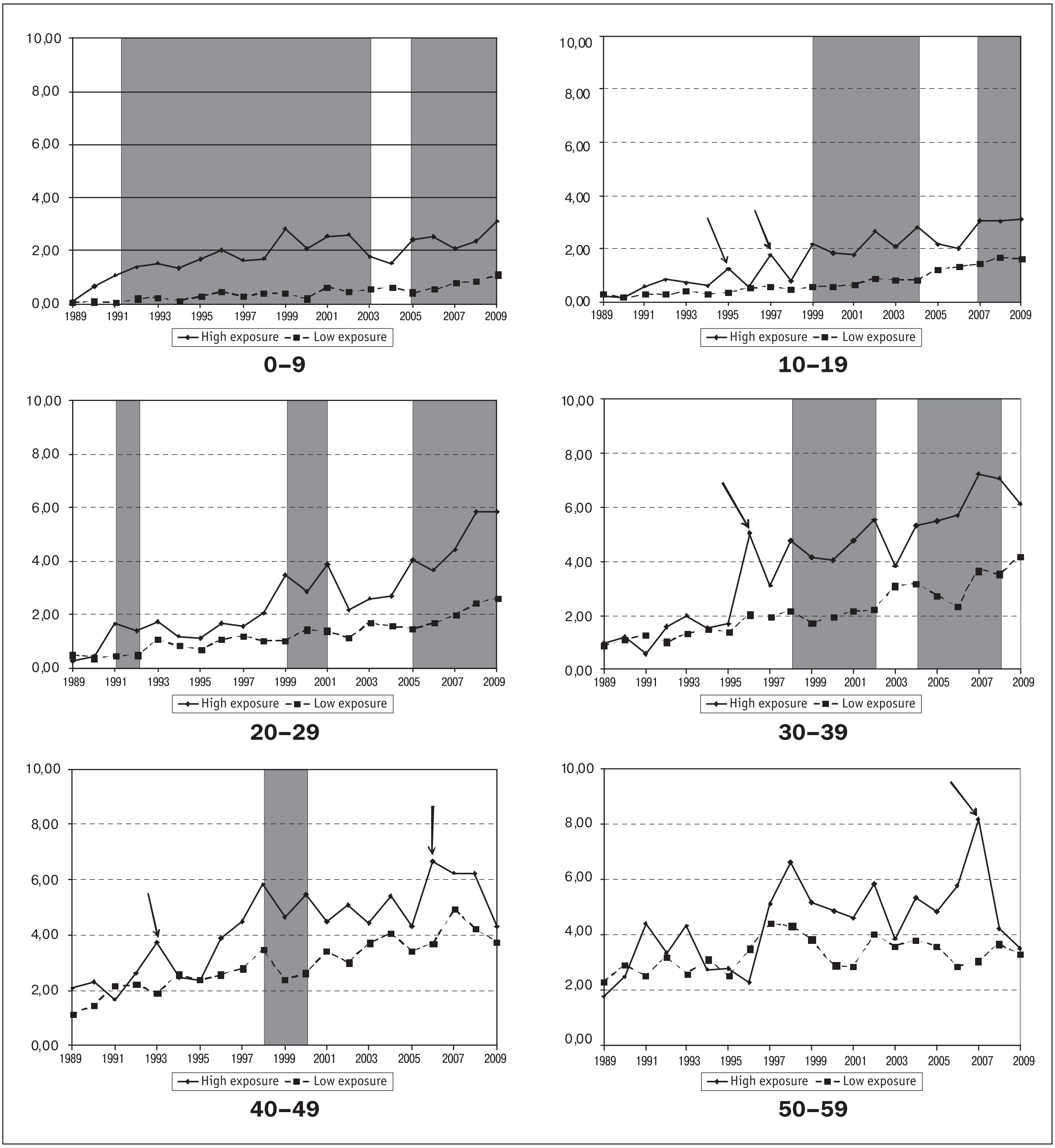

Figure 3. Trends of age-specific thyroid cancer incidence rates (per 10^5) in male population of "high" and "low exposure" regions of Ukraine (age in 1986)

Notes. X-axes indicate calendar years, Y-axes – age-specific thyroid cancer incidence rates (per 10^5); arrows and dark squares indicate years with significant difference between incidence rates of "high exposure" and "low exposure" regions

females. RR in male subpopulations was characterized by the annual fluctuations with very weakly expressed trends. Some increase of RR was observed in the group 30–39 (at the moment of the Chornobyl accident) since 1989 till 2002. In the rest male age groups i.e. 20–29, 40–49 and 50–59 it was rather difficult to define any long-term trend of increase or decrease for the RR.

In females the figures were more clear. In all age groups of 20 years old and more the RR somewhat tended to increase in the part of observation period with a following decrease. This value was the least expressed in oldest age group of 50–59 years old at the moment of the Chornobyl accident.

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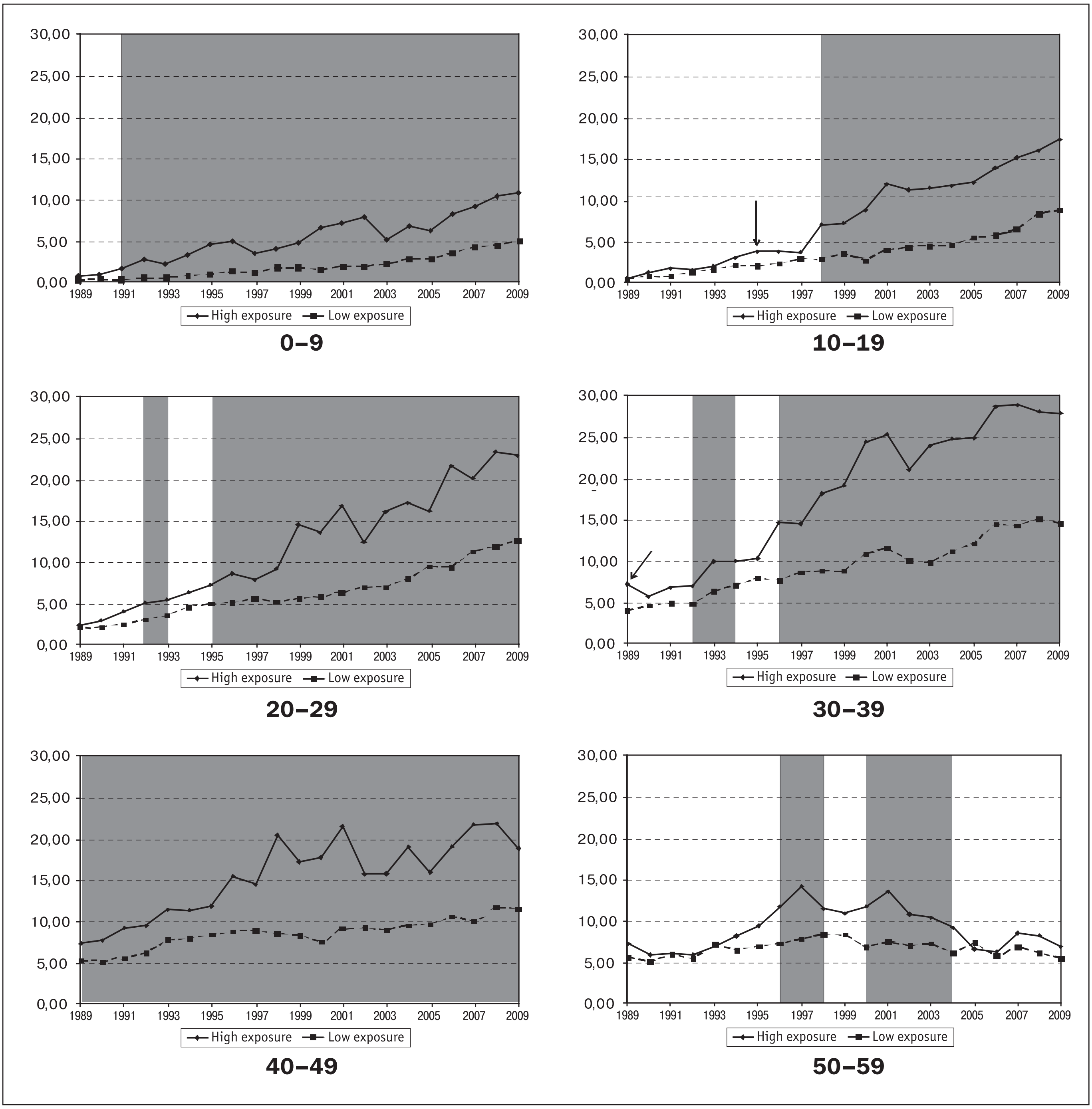

Figure 4. Trends of age-specific thyroid cancer incidence rates (per 10^5) in the female population of "high" and "low exposure" regions of Ukraine (age in 1986)

Notes. X-axes indicate calendar years, Y-axes – age-specific thyroid cancer incidence rates (per 10^5); arrows and dark squares indicate years with significant difference between incidence rates of "high exposure" and "low exposure" regions

DISCUSSION

Results of this study suggest a significantly higher increase of thyroid cancer incidence rate in population of "high exposure" territories comparing with "low exposure" ones (Fig. 2). Because different age groups should make different contribution in these trends a similar analysis for the specific age groups was very actual. It should be noted that in our opinion the elder age groups had drawn inadequately low attention from researchers. This statement was confirmed by a comparison of trends of thyroid cancer incidence rate between "high exposure" and "lower exposure" regions (Fig. 3, 4).

The results in age group 0–9 at the moment of the Chornobyl accident both in males and females confirmed the high vulnerability of thyroid to radiation in youth. Age-specific thyroid cancer incidence rates were significantly higher in "high exposure" regions since 1991 until the end of

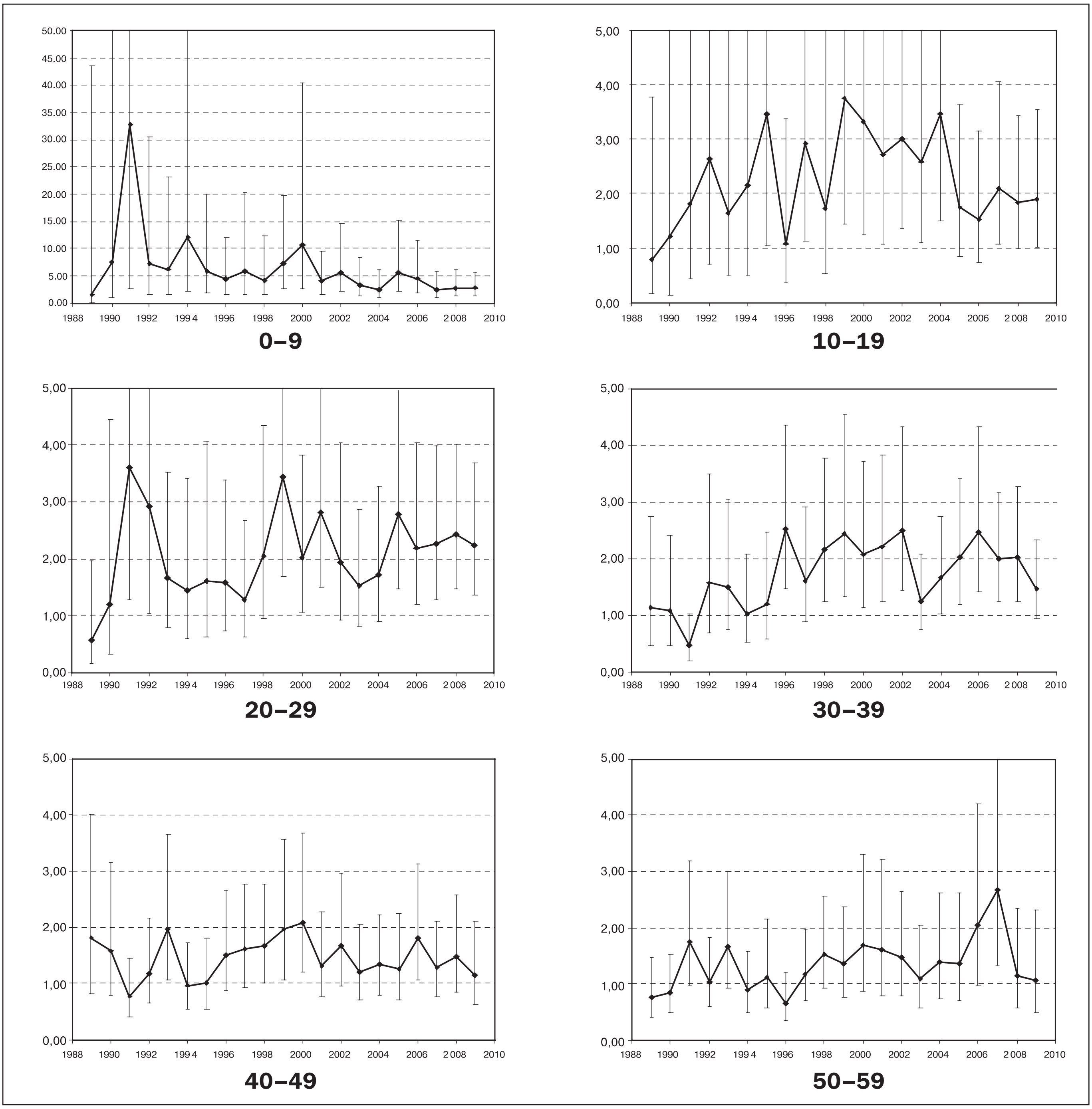

Figure 5. Trends of RR (rate ratio) between the age-specific thyroid cancer incidence rates in male population of "high" and "low exposure" regions of Ukraine (age in 1986)

Notes. X-axes indicate the calendar years, Y-axes – the RR

observational period. This figure is very characteristic for radiation carcinogenesis. In females it manifested more clearly.

As to a phenomenon revealed in female age group 40-49 it is very difficult to make any clear conclusions about its causation without additional information. It might be associated with some bias but also probably there is a specific character of this age that played some role as 40–49 years old is pre-menopausal and menopausal age. And in this age some hormonal alterations and disorders occur.

Hormonal factor as an etiology of thyroid cancer was a subject of interests of researchers. Higher thyroid cancer incidence rate in females is associated just with influence of estrogens. According to McTiernan et al. [32] the use of any of several estrogen-containing medications was associated with a bit increased risk of thyroid cancer. Imai et al. [33] found that endogenous estradiol was located in thyroid cancers much more frequently in females than in males. Analysis performed by

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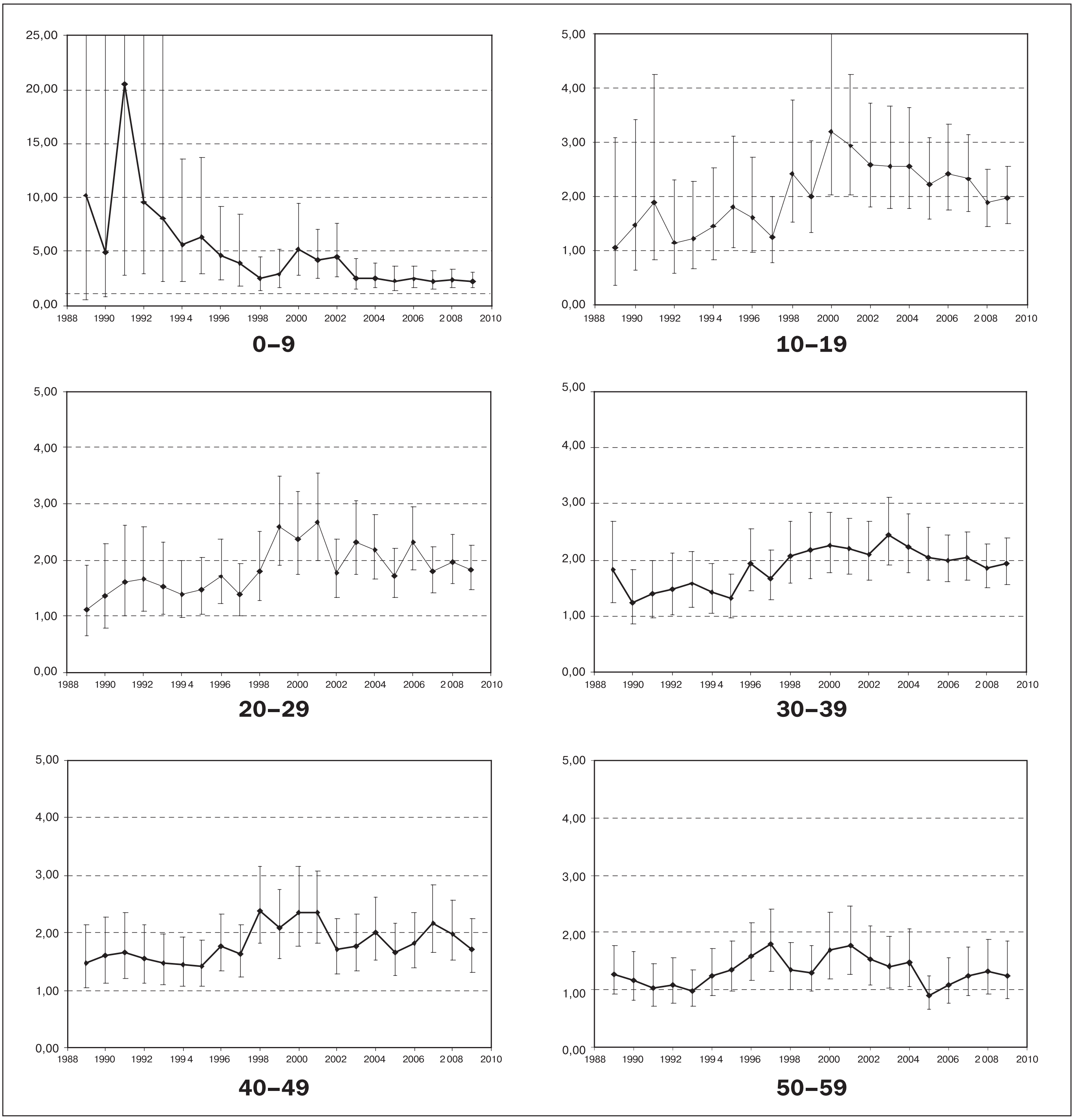

Figure 6. Trends of RR (rate ratio) between the age-specific thyroid cancer incidence rates in female population of "high" and "low exposure" regions of Ukraine (age in 1986)

Notes. X-axes indicate the calendar years, Y-axes – the RR

Farahati et al. [34, 35] demonstrates that the age-specific increase of thyroid cancer in females is related to puberty and consequently to estrogen production.

There is no enough information at present about a probable combined effect of hormonal status and radiation exposure on thyroid carcinogenesis. Anyway this issue needs further research.

Possible role of screening on registered thyroid cancer incidence should not be out of attention. Some opinion about possible existence or lack of screening effect can be received from information about frequency of ultrasound examinations of thyroid in "high exposure" and "low exposure" areas (table 1). This table shows that ultrasound diagnostic tests were made twice more frequently and more in "high exposure" territories comparing with "low exposure" areas. This certainly cannot be an immediate reflection of a role of screening effect on the regis-

Table 1

Frequency of thyroid ultrasound examinations in "high exposure" and "low exposure" areas

Area	Indexes	Years			
		1995	2000	2005	2006
"High exposure"	Number of ultrasound examinations	114 545	206 382	318 235	342 051
	Number of population	10 071 240	9 762 215	9 421 375	9 393 874
	Frequency per 10^5	1137.3	2114.1	3377.8	3641.2
"Low exposure"	Number of ultrasound examinations	217 176	472 339	594 958	652 325
	Number of population	41 402 467	39 692 494	37 679 087	37 355 296
	Frequency per 10^5	524.5	1190.0	1579.0	1746.3
Ratio between frequencies of ultrasound examinations in "high exposure" and "low exposure" areas		2.17	1.78	2.14	2.09

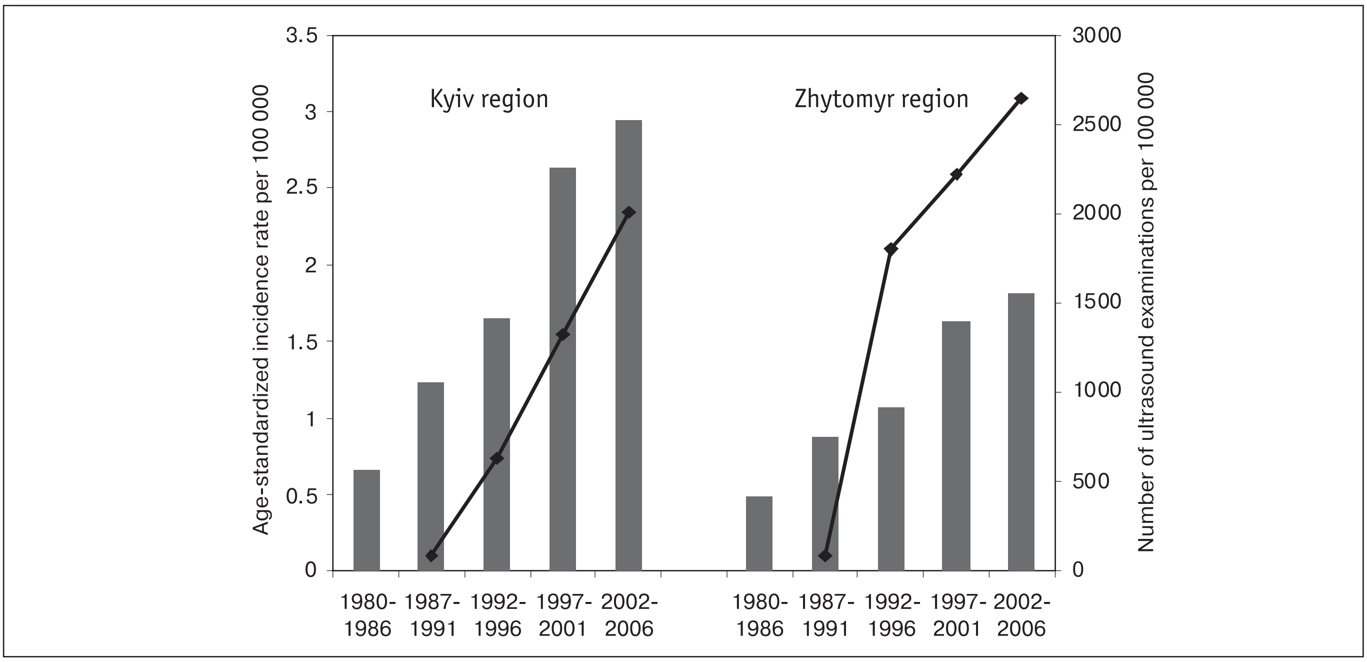

Figure 7. Age-standardized average annual thyroid cancer incidence rates in Kyiv and Zhytomyr regions for different time periods (males) and frequency of ultrasound examinations

tered thyroid cancer incidence rate. Next example is quite illustrative (Fig. 9).

This figure presents data on thyroid cancer incidence rates since 1980 (bars) and frequency of ultrasound examinations per 100 000 (lines) in Nothern regions (Kyiv and Zhytomyr) with relatively high doses on thyroid. It is very striking that the thyroid cancer incidence rate in Zhytomyr region was lower than in Kyiv one, but number of ultrasound examinations per 100 000 population there was higher.

Another suggestion for a quite weak effect of more frequent usage of ultrasound diagnostic procedure on registered thyroid cancer incidence is the fact that in "high exposure" regions the 73.1 % from total number of thyroid cancer cases were diagnosed in 2006 at I-II stages whereas in the rest regions of Ukraine this index was 68.3 % [36]. These examples give background to certify that this procedure does not influence significantly on figures of the registered thyroid cancer cases.

CONCLUSION

Results of this study have confirmed the radiation excess of thyroid cancer in children and adolescents at the time of the Chornobyl accident due to exposure to radioactive iodine. This study also suggested the increased risk of occurrence of thyroid cancer in adult age groups of population residing in "high exposure" territories. This excess was less expressed in elder age groups and manifested after more prolonged period probably due to a longer latency period.

The additional studies are necessary to clarify the origin of thyroid cancer excess in females aged 40–49 and living in "high exposure" regions. Hypothesis of a combined effect of radiation and natural changing of hormonal status in this age should be tested.

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