SCIENTIFIC ARTICLES

Dynamics of thyroid cancer incidence in Russia following the Chernobyl accident: eco-epidemiological analysis

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The paper presents the analysis of thyroid cancer incidence in the territories of Russia that were most contaminated after the Chernobyl accident. Incidence data in the Bryansk, Kaluga, Orel and Tula regions (5,298 thousand persons) are used.

Information on incidence has been obtained from regional oncological dispensaries (state health institutions involved in diagnosis and treatment of malignant neoplasms). Altogether, 2,599 cases of thyroid cancer are considered from 1982 to 1995. Of them, 62 cases were among children and adolescents and 143 among the population who were children and adolescents at the time of the accident in 1986. The study is performed for both sexes.

The study compares the distribution of thyroid cancer cases by age at diagnosis and age at exposure. It has been shown that since 1991 the age structure of the incidence has changed significantly with the growing proportion of cases among children and adolescents. The change in the structure occurred due to the radiation factor, specifically as a result of exposure of thyroid to incorporated ^{131}I. A dependence of risk of cancer on age at exposure has been derived. For children of 0-4 years at exposure the risk of induction of radiogenic thyroid cancer is 6-10 times higher than in adults. On the average, the risk co-efficient in children and adolescents at the time of exposure is about 3 times higher than that in adults.

The analysis of time trend in thyroid cancer incidence has shown that the incidence rate observed in the period from 1991 to 1995 in the age groups up to 25 years is expected to be maintained in the near future.

Introduction

As a result of the Chernobyl accident extensive areas of Russia (more than 60 thousand km^2) were affected by the radioactive contamination. The most contaminated was the territory of western areas of the Bryansk region where the maximum density of ^{137}Cs soil contamination is as high as 4 MBq/m^2. Somewhat lower, yet a rather significant contamination was reported in the Kaluga, Tula and Orel regions. The maximum soil contamination with ^{137}Cs in these areas was 0.6 MBq/m^2.

The most significant distant medical consequences are exposure of thyroid in the residents of the contaminated areas to incorporated ^{131}I which enters the body by inhalation or per orally. This problem is particularly urgent for those residents of the contaminated areas who were children and adolescents during the exposure, as the risk of developing cancer (as well as dose) is strongly dependent on the age at exposure.

Unfortunately, to date no detailed picture of ^{131}I depositions in the territory of Russia is available, but the maximum ^{131}I deposition density in Bryansk region is known to be 15 MBq/m^2, as of 10 May 1986.

Under these circumstances it is of particular importance to conduct epidemiological analysis of thyroid cancer incidence in the population of the most contaminated regions of Russia (Bryansk, Kaluga, Tula, Orel).

There are a large number of publications on radiation induced thyroid cancers [1-3]. These publications also include all necessary references. However, most of these studies focus on the effects of external exposure on thyroid cancer incidence. The effect of internal irradiation of the thyroid in children and adolescents due to incorporated to ^{131}I was studied in references [4-7] based on a limited number of cases (2-6 cases). For these reasons the derived estimates are characterized by significant errors.

The purpose of the present work is to analyze the dynamics and structure of thyroid cancer incidence in four regions of Russia with the population of 5,298 thousand people in 1982-1995. The analysis is based on data of 2,599 cases of thyroid cancer during this period of time. Of them, 62 cases were among children and adolescents at the time of diagnosis and

143 cases among the population who were children and adolescents at the time of the accident in 1986. Since individual radiation doses cannot be estimated on such a large scale, an eco-epidemiological method is used.

One of the major limitations of the approach used is a possible bias in the derived values of radiation risk due to changing intensity of screening of thyroid cancers in the post-Chernobyl period and in the determination of "controls". For this reason, the work places particular emphasis to these matters. At the same time, an advantage of the approach is taking into account of all detected cases of thyroid cancer in the four most contaminated regions of Russia to estimate indicators of incidence in different age groups prior to the Chernobyl accident and after it.

Methods and materials

General description of medical and demographic data

The primary source of demographic information was the data of federal state statistic bodies and regional statistic committees. Table 1 shows the demographic characteristics of the population in the Russian regions under consideration in 1986 (at the time of the Chernobyl accident).

Table 1

Population in the regions of Russia that were studied

Region	Bryansk	Kaluga	Tula	Orel	Total
Number of children (0-14 years) and adolescents (15-17 years), thousand					
Boys	190	132	197	102	621
Girls	184	127	190	96	597
Number of adults, thousand					
Males	481	376	633	320	1810
Females	615	458	801	396	2270
Mean age of population					
Males	33	34	36	36	35
Females	40	40	42	42	41

Table 2

Number of thyroid cancer cases among residents of the Bryansk, Kaluga, Tula and Orel regions

Region	Bryansk	Kaluga	Tula	Orel	Total
Number of cases among children and adolescents at diagnosis (1982-1985)					
Boys	0	0	0		0
Girls	2	0	0		2
Number of cases among adults at diagnosis (1982-1985)					
Males	20	4	14	12	50
Females	81	48	115	67	311
Number of cases among children and adolescents at diagnosis (1986-1990)					
Boys	3	0	0	0	3
Girls	1	1	2	1	5
Number of cases among adults at diagnosis (1986-1990)					
Males	41	15	26	26	108
Females	280	50	181	135	646
Number of cases among children and adolescents at diagnosis (1991-1995)					
Boys	12	2	4	1	19
Girls	20	2	5	6	33
Number of cases among adults at diagnosis (1991-1995)					
Males	70	20	75	42	207
Females	417	98	422	278	1215
Number of cases among children and adolescents at exposure					
Boys	21	3	11	4	39
Girls	40	5	26	33	104

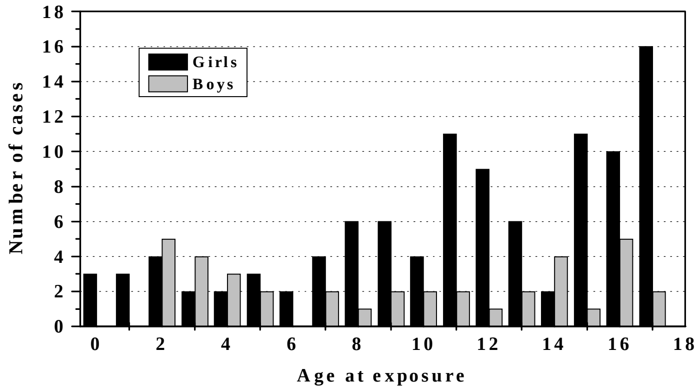

Fig. 1. Number of cases as a function of age at exposure.

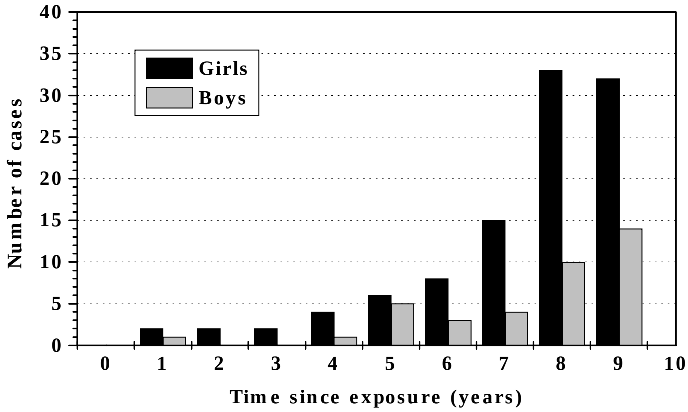

Fig. 2. Number of cases as a function of time after exposure.

Table 2 contains the number of detected cases of thyroid cancers as a function of region, time interval and age during diagnosis and age at exposure. These are official data of oncological dispensaries in Bryansk, Kaluga, Tula and Orel regions in charge of registration of oncological patients in accordance with regulations of Ministry of Health of Russia. A total of 2,599 cases were detected from 1982 to 1995. Among them 2,212 cases are among females (40 cases among girls of 0-17) and 387 cases among males (22 cases among boys of 0-17).

There were 143 cases among persons born in 1969-1986, who were children and adolescents at the time of exposure (39 boys and 104 girls). Figures 1 and 2 shows the number of cases among children and adolescents at the time of exposure as a function of age during exposure and the time after exposure.

Among the children born (after the accident) from 1987 to 1995 no cases of thyroid cancer have been reported (the beginning of the period is chosen to include fetal exposure). The most common kinds of cancer among the population of the above four regions of Russia in 1982-1995 were papillary and follicular cancers (43% and 44% in males and 47% and 44% in females, respectively, of the total number of cases).

Figure 3 shows the relation of the frequency of thyroid cancer incidence in females to that in males in different age groups in Russia and some known cancer registries [8, 9]. In Figure 4 the value of this ratio is given for the whole of Russia and for the population of the four regions under consideration. For Russia as a whole the frequency ratio attains a maximum of 6 in the age range of 35-39 years. For other cancer registries, the maximum of the ratio occurs in the age range of 24-29 years.

As can be seen from Figure 4, the female/male ratio of frequency of thyroid cancer in Russia as a whole and the four contaminated regions is in agreement within a standard error.

The dynamics of thyroid cancer incidence in the study regions in comparison with Russia is presented in Figures 5 and 6. Figure 5 presents a standardized ratio of incidence with 95% confidence intervals (SIR

= observed number of cases/expected number of cases) for each region separately and Figure 6 - for all four regions altogether. The confidence levels are calculated according to [10].

The dynamics of the Standard Incidence Ratio (SIR) in 1982-1995 in Bryansk, Tula and Orel regions (Figure 5) reveals an interesting feature. This feature is evident from Figure 6 showing the dynamics of the SIR for the four regions. Indeed, in 1982-1986 the thyroid cancer incidence, both in males and females, was lower than in Russia (Russia as a whole is taken as control). In 1982-1986 SIR was < 1. In the second period 1987-1991, as can be seen from Figures 5 and 6, SIR, on the average, is more than 1, i.e. the incidence in the four regions becomes higher than in Russia as a whole. As the period 1987-1991 is a latent period for induction of thyroid cancer by radiation, the growth of incidence in this period can be attributed to introduction of a specialized examination system in these regions (the screening effect). As can be seen from Table 2 in the above four regions in the period 1982-1985, on the average, 90 cases of thyroid cancers were reported and in 1986-1990 152 cases were detected annually (1.6 times higher). It is interesting to note that in the previous work on thyroid cancer among Chernobyl accident emergency workers [11] we also demonstrated the screening effect with the coefficient of 2.6. After 1991, as can be seen from Figure 6, a certain growth of thyroid cancer incidence in the four regions of Russia under study is observed.

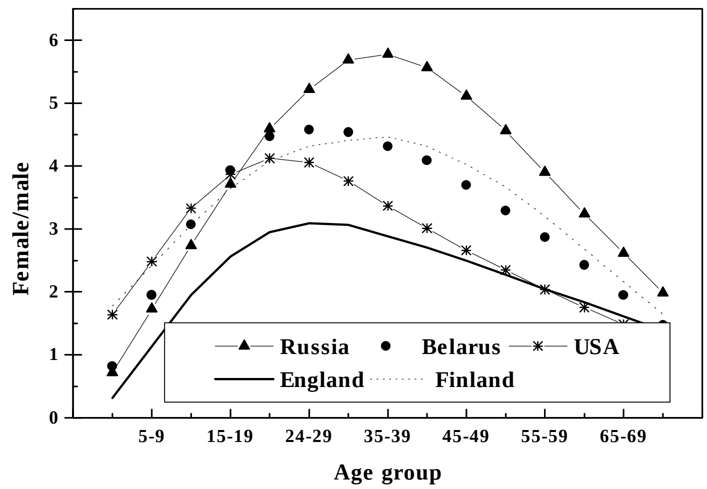

Fig. 3. Female/male ratio of thyroid cancer incidence as a function of age at diagnosis in Russia and using data of world cancer registries.

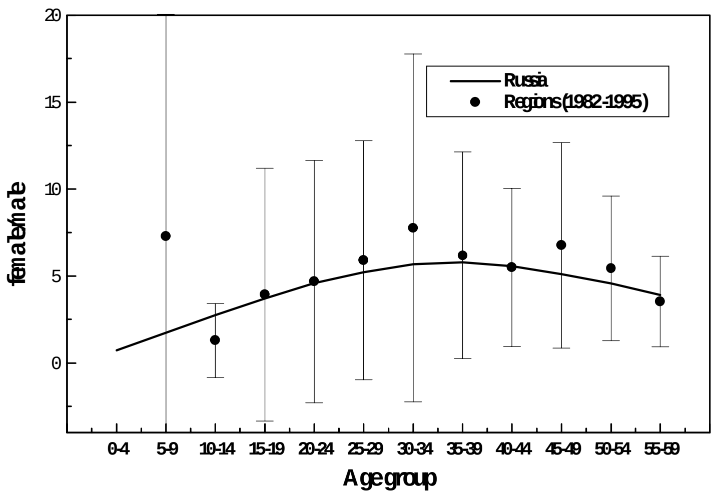

Fig. 4. Female/male ratio of thyroid cancer incidence as a function of age at diagnosis in Russia as a whole and among the population of the four regions.

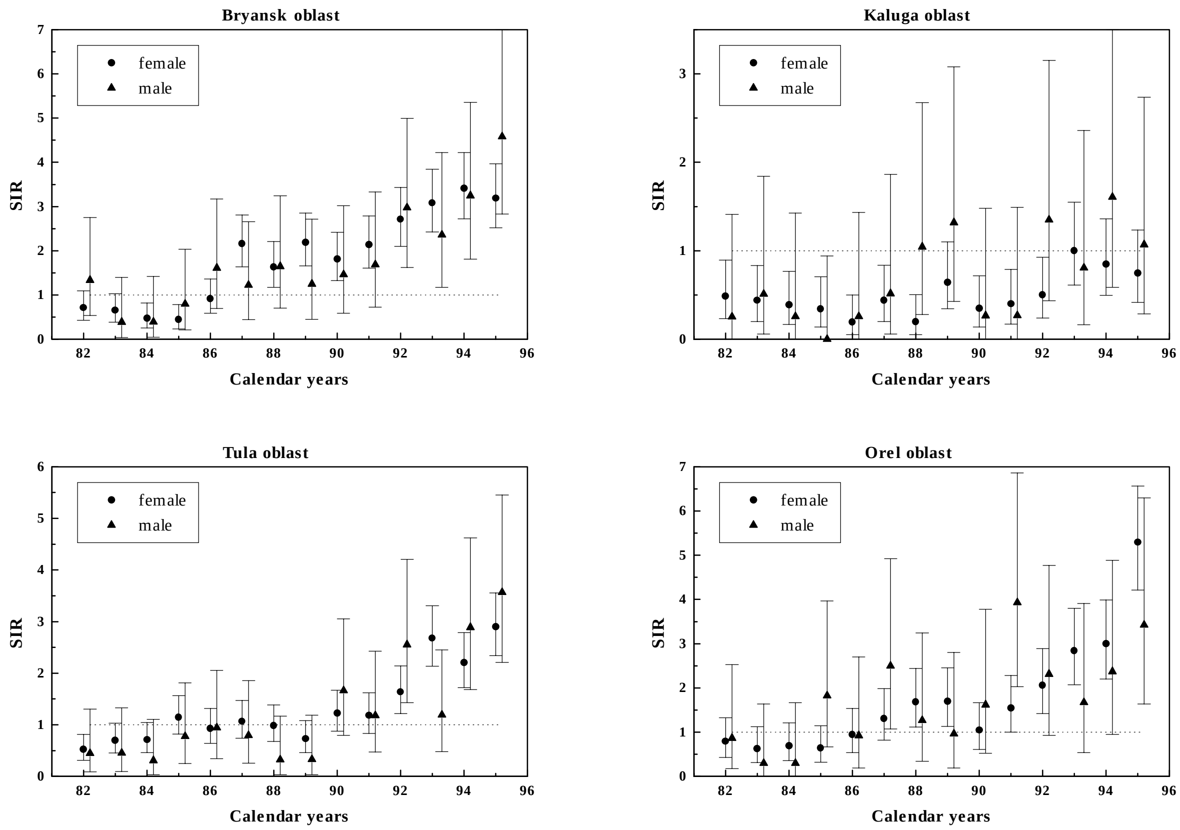

Fig. 5. Dynamics of standardized thyroid cancer incidence ratio in Bryansk, Kaluga, Tula and Orel regions (ration control - Russia).

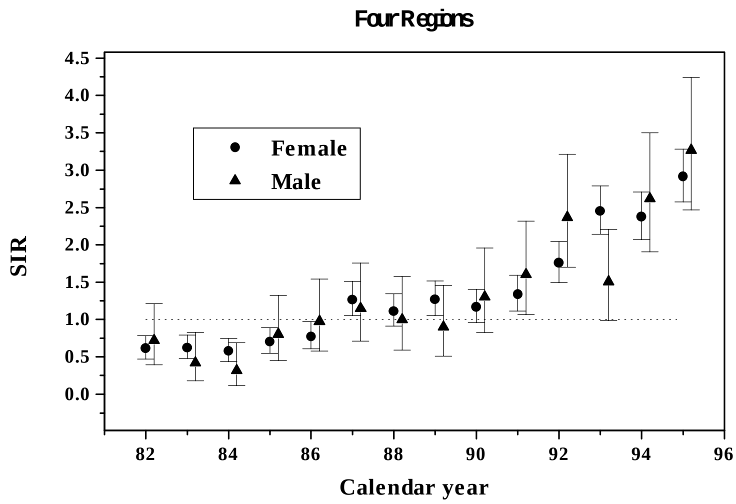

Fig. 6. Dynamics of standardized thyroid cancer incidence ratio in the four regions under consideration together (ration to control - Russia).

Methodology of the study

The main idea of the present study is the comparison of age distributions of thyroid cancer cases in exposed and unexposed (control) populations. The risks of induction of radiogenic cancers at the same dose and dose rate are known to depend on age at exposure [12, 13]. For malignant neoplasms at most sites, the decrease in age at exposure leads to an increase in the risk of cancer. This equally applies to radiogenic thyroid cancer [1-3]. The above risk dependence will be better defined in case of thyroid exposure to incorporated ^{131}I, as in this case; the thyroid exposure dose will depend on age at exposure [12, 14, 15]. So, induction of radiogenic cancers should change the shape of age distribution of cancers.

The regions of Russia under study (Bryansk, Kaluga, Tula and Orel regions) are similar in geography, demography and socio-economical development. The data of state statistics suggest that the sex-age structure of the population in the post-accident period in the regions under study and Russia in general remained practically unchanged. Therefore, it can be expected that dependencies of thyroid cancer incidence on age prior to exposure and in the latent period of radiogenic cancer development will be close to dependencies for the Russia in general. Besides, it may be assumed that the observed regional difference in thyroid cancer incidence in the regions under study, accurate to a constant factor, does not change the distribution form. Of course, the question arises as to the quality of data on thyroid cancer in Russia used as control and on the objectivity of assumptions concerning distribution forms. For analysis of data quality, we use such information of medical statistics in Russia for 1993 [8] and world oncological statistics [9]. Information on thyroid cancer incidence for major cancer registries of UK, USA (SEER, whites), Belarus and Finland for 1983-1987 was borrowed from [9]. Figure 7 shows the distribution density $f(x_i) = \dfrac{\lambda_i}{\lambda_i^0}$ with respect to age, where λ_i is incidence rate in the ***i***-the age group of a specific country; λ_i^0 is incidence indicator in the ***i***-th age group of the country selected as control. We took the registry of UK as a control for the analysis of the completeness of Russian data. This control was selected because the cancer registry of UK is fairly representative (about 50 million people) and covers a long observational period (we used data for 1978-1987) [9, 16]. Besides, the analysis of incidence distribution by age in the British registry in 1978-1982 and 1983-1987 has shown a very close agreement in distributions, which suggests the reliability of this registry data. Different age ranges in Figure 7 (5-60 years for males and 10-60 years for females) are due to the data available in [9].

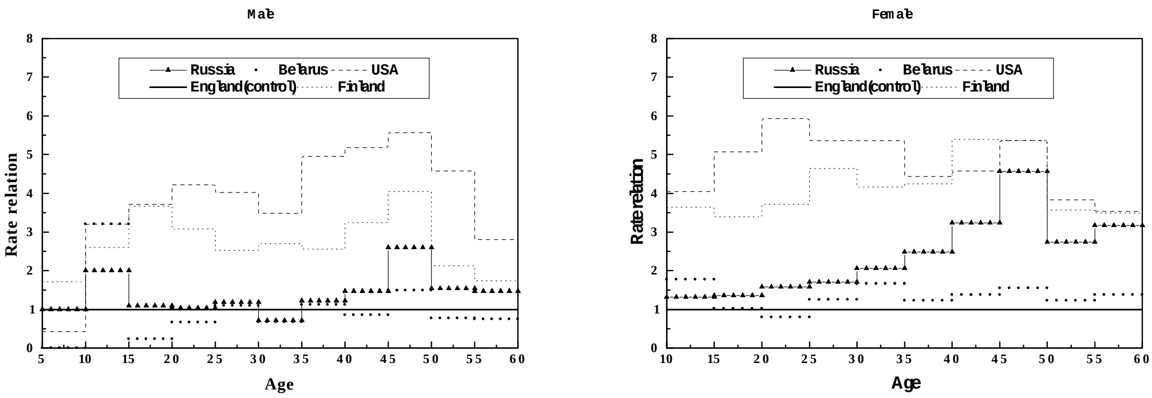

Fig. 7. Density distribution of thyroid cancer incidence ratio as a function of age.

Within the hypothesis proposed above about stability of the forms of the incidence age distribution, the ratio of rates of thyroid cancer incidence characterizes detectability of cancer in different age group with respect to control. It can be seen from Figure 7 that for most age groups the detectability is almost identical for a given registry, though the value is different from the control value, this difference can be attributed to both the difference in detectability levels for the population in general and to the difference in actual incidence levels. The exception is distribution for females of Russia. The maximum (45-49 years) and minimum (10-14 years) ratio of incidences in this case differ by a factor of 3, while the detectability with respect to the control increases monotonically to the age of 45-49 years, at which the incidence according to the data of Russian statistics is maximum too.

The above distributions can be used to estimate a potential effect of in-depth screening. It is unlikely that the maximum detectability of cancer is due to hyper diagnosis. Therefore, the ratio of maximum and minimum detectability for a specific country can serve as an estimate of a potential screening effect with respect to the control in different age groups.

In addition to distribution density, we use the function of distribution by age for analysis of oncological information:

$$F(x_i)=\frac{\sum_{k=1}^{i} f(x_k)\times \Delta u_k}{\sum_{k=1}^{N} f(x_k)\times \Delta u_k},$$

Where i=1,2,...,N and N is the number of age intervals; Δu_k is width of the k-th age interval.

Unlike for density, we compensate for possible regional differences in actual incidence and cancer detectability in the distribution.

Figure 8 shows one age distribution (up to 60 years) of incidence rate ratios for different registries. It is obvious that for the control population (UK registry) the distribution density will be uniform and the distribution - linear. The linear form is convenient for comparison and analysis of cancer data quality. It can be seen that, by and large, the distributions for males are close (including those for Russia). The exception is the distribution for the USA population. For this registry the distribution is close to linear (detactability in different age groups is about the same) and the difference is primarily due to the shift (lack of data) in the age group of 5-9 years. For females all distributions, except Russia, are well consistent. The reasons of the difference in the Russian distribution possibly relate to poor cancer detectability young age.

The similarity in age structure of incidence for the registries under consideration is also confirmed by the mean age of cancer development $\overline{u}$ (Table 3) derived from the ratio:

$$\overline{u}=\frac{\sum_i \lambda_i * i}{\sum_i \lambda_i},$$ summation is made by all ages i to 60 years.

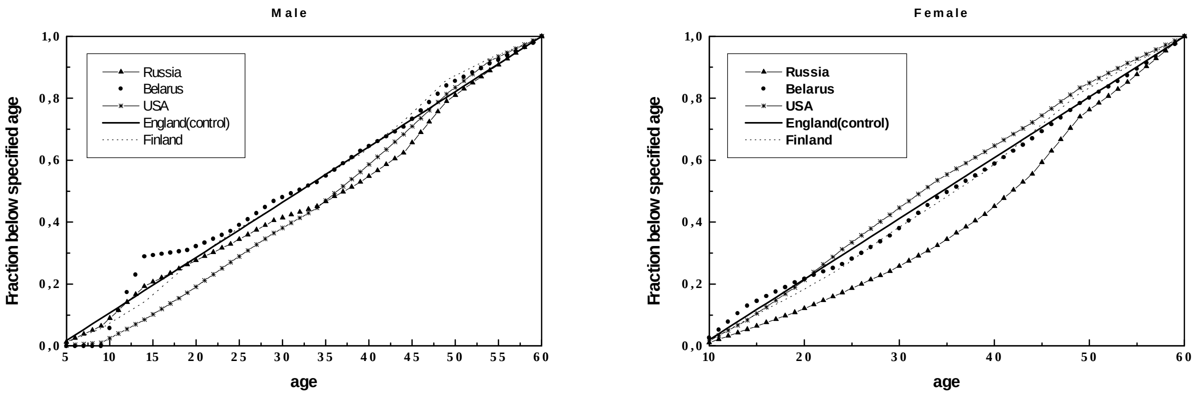

Fig. 8. Distribution of thyroid cancer incidence ratio as a function of age (to 60 years).

Table 3

Mean age of thyroid cancer development according to data of different cancer registries (age to 60 years)

Countries	Males	Females
Russia	52.6	49.2
Belarus	54.3	48.9
UK	49.7	44.4
USA	52.1	47.9
Finland	52.5	46.8

As the form of the theoretical distribution in the population, selected as control, is known to be linear, it is convenient to use the Kolmogorov criterion as a criterion of agreement between the selected and theoretical distributions [17]. In calculations of probability P that the maximum discrepancy between the selected distribution $F^*(x)$ and the theoretical distribution $F(x)$ in the control population will be not less than the observed one, the value $\alpha = D\times\sqrt{N}$ is used as a parameter. D is defined by the quarter $D=max\left|F^*(x)-F(x)\right|$ - or in words, the maximum of the module of difference between the selected and theoretical distribution function and N is the number of age distributions. Calculations of P for different registries are presented in Table 4.

As the risk of induction of radiogenic cancers at thyroid exposure to incorporated ^{131}I is strongly dependent on age at exposure and increases at young, age we study the quality of data on incidence for the age less than 30 years. As is shown in [12, 14, 15], for older age the thyroid dose is practically independent of age and determined by the amount of incorporated radionuclides only. The distribution functions for incidence ratios in this range and ***P*** values are presented in Figure 9 and Table 4.

It can be seen from the data presented thus, that for females in the Russian population the distribution in the age range 5-30 years is in good agreement with the control and most of other registries. For males the agreement is not that good, which is probably because of rare cases of cancers. However, the value of probability ***P*** for incidence distribution among males of Russia is close to unity (0.99).

Most of the registries under consideration do not include data on incidence for the range of 0-4 years, in which the effect of radiation exposure to the thyroid may be maximum except for information on boys in the UK registry and Russian data obtained for the whole population of Russia (this age group includes about 11 million people). The comparison of Russia data with the data of UK registry shows that the value ***P*** for the range 0-30 years is rather considerable: 0.86.

The above results show that in the age range to 30 years the data on thyroid cancer incidence included in the state medical statistics of Russia can be used as a control in this study. Hereinafter, “control” will be understood as one Russian population.

Table 4

***P* probability values for different registries**

Sex	Males		Females	
Age interval	5-30	5-60	10-30	10-60
Russia	0.99	0.68	0.99	0.12
Belarus	0.18	0.51	0.97	0.99
USA	0.47	0.68	0.99	0.99
Finland	0.99	0.99	0.99	0.99

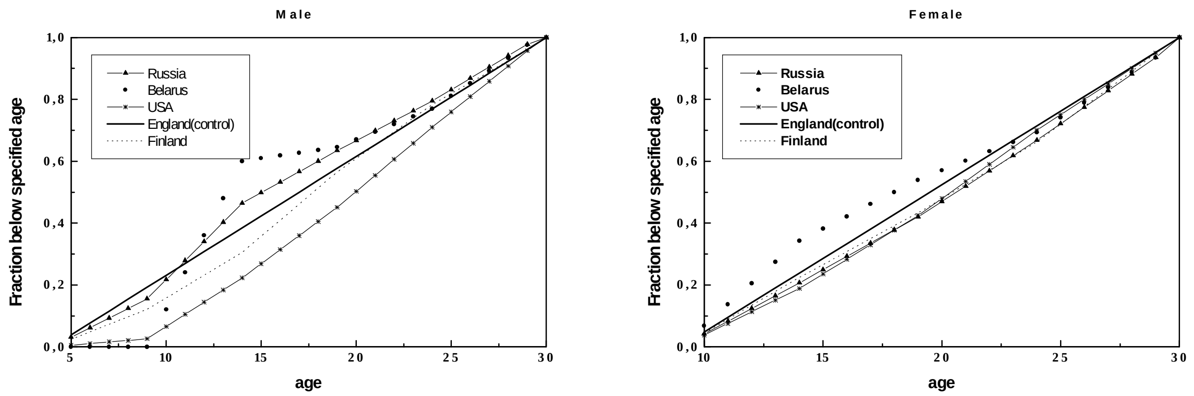

Fig. 9. Distribution of thyroid cancer incidence ratio as a function of age (to 30 years).

Results

The data on thyroid cancer cases in 1982-1995 in the territories under study were represented as a matrix M_{ij}, index ***i*** is age at diagnosis or age range and ***j*** is time after exposure.

Each matrix element is the ratio of thyroid cancer rate in the age group under study at a certain time moment and control - the population of Russia $\frac{c_{i,j}}{\lambda_{i,j} \times n_{i,j}}$, where $c_{i,j}$ is the number of cases at age ***i*** in ***j*** years after exposure; $n_{i,j}$ is number of age group ***i*** in ***j*** years after exposure; $\lambda_{i,j}$ is thyroid cancer rate in Russia.

Two time intervals were considered: the first period from 1982 to 1990 included a pre-accident time period from 1982 to 1986 and the latent period of 5 years from 1986 to 1990 inclusive. This was assumed to be the period of spontaneous cancers. The second (postlatent) period covered from 1991 to 1995 when radiogenic cancers could be induced. The age scale for this period starts from 5 years to exclude children born after the accident. The correctness of dividing into the above time intervals is confirmed by the dynamics of standardized incidence ratio (SIR) of thyroid cancer in the regions under study as compared to Russia (Figure 6).

The results of calculating distributions of incidence relations in the regions under study and Russia as a function of age (age at diagnosis) and calendar period are shown in Figure 10. It can be seen that after 1991 a radical change occurred in the age structure of thyroid cancer incidence for the considered age range and the distribution in this time period differs considerably from the Russian one. The curve shape in the period after 1991 (above the Russian distribution) reflects a considerable increase in incidence at younger age as compared to Russia. On the other hand, for older age the distributions in the time periods under consideration are about identical, for example, for females of 30-50 years (Figure 11).

This result is confirmed by SIR for all the regions that are considered as function of age at diagnosis, as is shown in Figure 12.

Thus, in the post-latent period, a radical charge in age structure of thyroid cancer incidence occurs for children and adolescents.

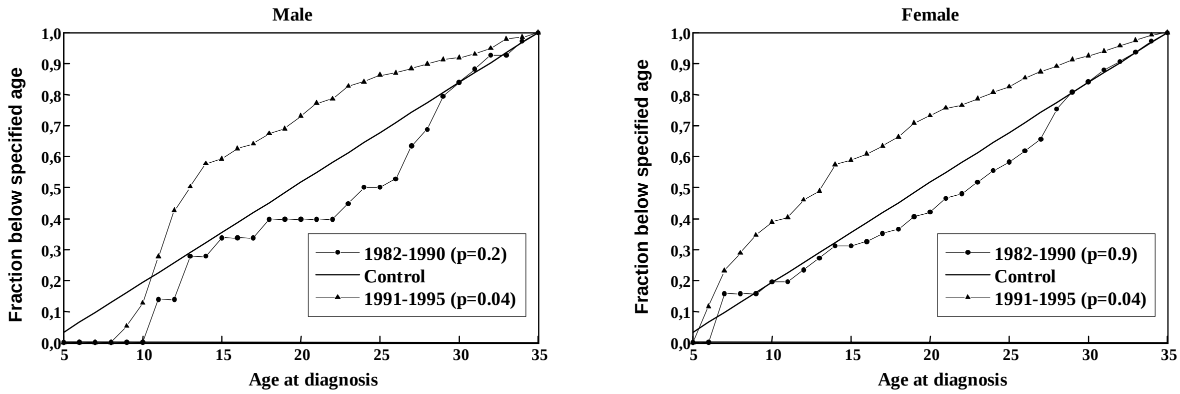

Fig. 10. Distribution function for thyroid cancer incidence ratio as a function of age and sex.

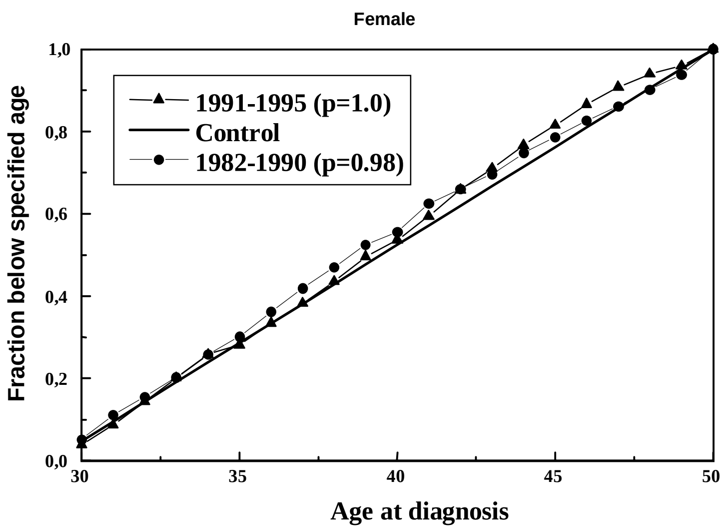

Fig. 11. Distribution function for thyroid cancer incidence ratio among females as a function of age (30-50 years).

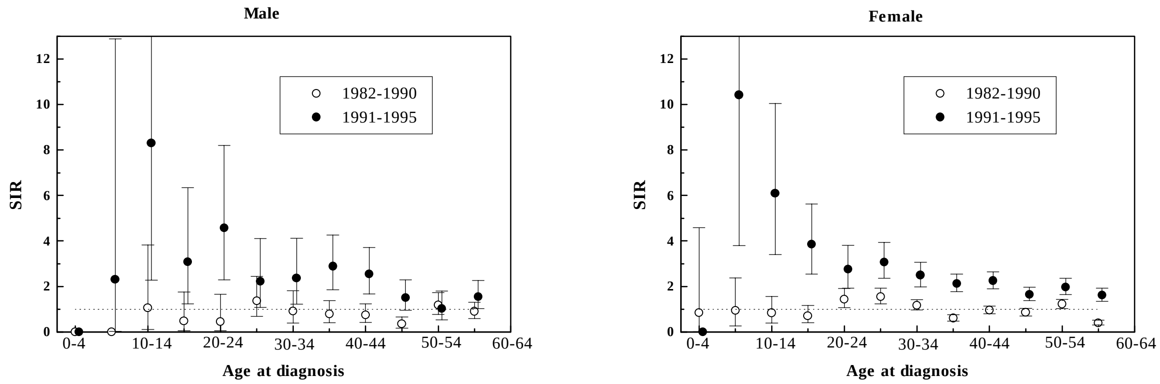

Fig. 12. SIR distribution as a function of age at diagnosis.

If this is a consequence of radiation exposure to the thyroid, then changes in age structure of incidence should be maximum for those who were children and adolescents at exposure time.

To prove this statement we use two time intervals: the first ***m***=9 years (1982 to 1990) and ***n***=5 years (1991 to 1995). Let us consider the ratio of observed and expected (in Russia in general) incidences in the considered time intervals among individuals of age ***i*** at the beginning of each time interval:

$$RR_i = \frac{observed_i}{expected_i} = \frac{\sum_k c_{i,i+k}}{\sum_k \lambda_{i,i+k} \times n_{i,i+k}},$$

k=0,1,...,***m*** for the first observational, ***k***=0,1,...,***n*** for the second, and (***i+k***) is age diagnosis. The quantity of RR_i for individuals of age ***i*** in 1986 is an estimate of relation of relative risk of induction of radiogenic cancer and age at exposure.

Figure 13 presents the results of calculating the risk of induction of radiogenic thyroid cancer in children and adolescents with respect to adults with 95% confidence intervals. The risk distribution is normalized to the mean-weighted risk among adults with consideration of size of corresponding age groups. It should be noted that with such normalization the regional differences in incidence are compensated.

The summation of ***RR*** relation over all the regions is competent in this case, as the age structure of population is approximately the same and distributions of ***RR*** for each region will be similar with accuracy to a constant factor describing the total contamination of the region with ^{131}I. The 95% confidence intervals have been calculated according to [10].

In [12, 14, 15] the relation of thyroid dose ***D*** and unit activity of incorporated ^{131}I has been derived as a function of age at the time of the Chernobyl accident. It has been shown that the difference in absorbed doses of younger age groups can occur earlier than at the age of 20-24 years at exposure. The distribution of dose ***D*** is also shown in Figure 13. The dose is normalized to unity at age at exposure 20-24 years.

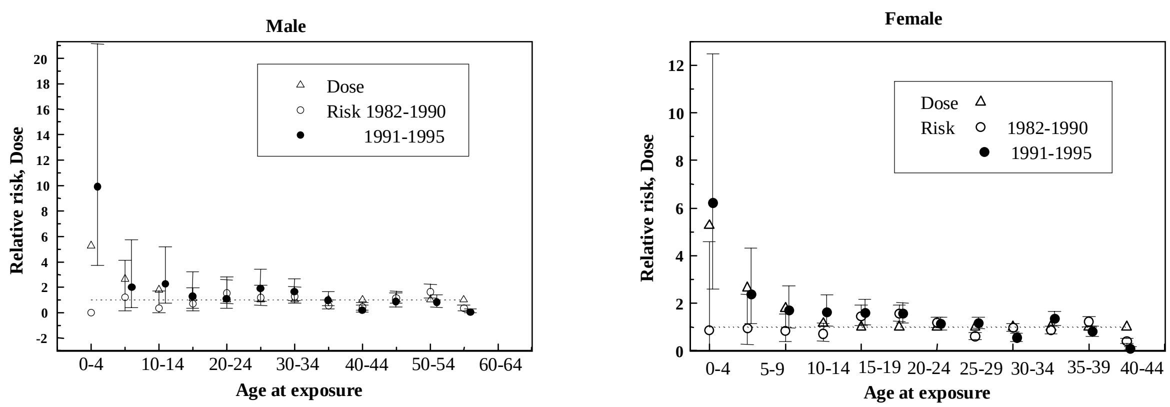

Fig. 13. Ratios of risks (***RR***) and doses (***D***) as a function of age at exposure and calendar period.

It can be seen that the relations for both sexes in the period of spontaneous cancers are close to unity and differ significantly from unity in the assumed period of induction of radiogenic cancers (1991-1995) for children and adolescents. The points on the plot are shifted to reveal the bias in the values. The shape of the curve of relative risk in post latent period is in good agreement with the dose ratio.

As is seen from Figure 13, the relative risk of induction of radiogenic cancer for children of 0-4 years age at exposure is 6-10 times and for those of 5-9 years - 2-3 times higher the risk for adults in the considered period 1991-1995. The values of risk for both sexes are approximately the same, which is in agreement with result of [1-3, 18]. The comparison of the presented distributions of relative risk and dose distribution leads us to conclude that the excessive risk among children and adolescents in the considered time period after exposure is primarily due to a high dose, rather than an increased radiation sensitivity.

The above results give enough grounds to assume that the change in the age structure of thyroid cancer incidence between 1991 to 1995 is attributed to the radiation factor. A convincing evidence of this is the fact that among the children born after 1987 falling in the age range of 0-9 years at diagnosis no thyroid cancer cases have been detected as compared to 7 cases among children born prior to the accident and falling in the same age range after 1986, given similar screening depth and coverage.

Clearly, it is important to study time trends in thyroid cancer incidence. Figure 14 shows linear trends (with 95% confidence intervals) in cancer incidence as a function of age at exposure and calendar period. In calculations we used a standard procedure of the weighted least square method. To assign a larger weight to observations with a lesser variance a weighting factor in inverse proportion to variance was used. As follows from the figure, the linear trend in the first period (1982-1990) is close to zero in most age groups and is more than zero in the post latent period, though the statistically significant difference is reported in the group 0-4 for boys and in the group 15-19 for girls.

The presented results make us to conclude that at least in the near future one should not expect a noticeable increase in thyroid cancer incidence rate in the age groups under study.

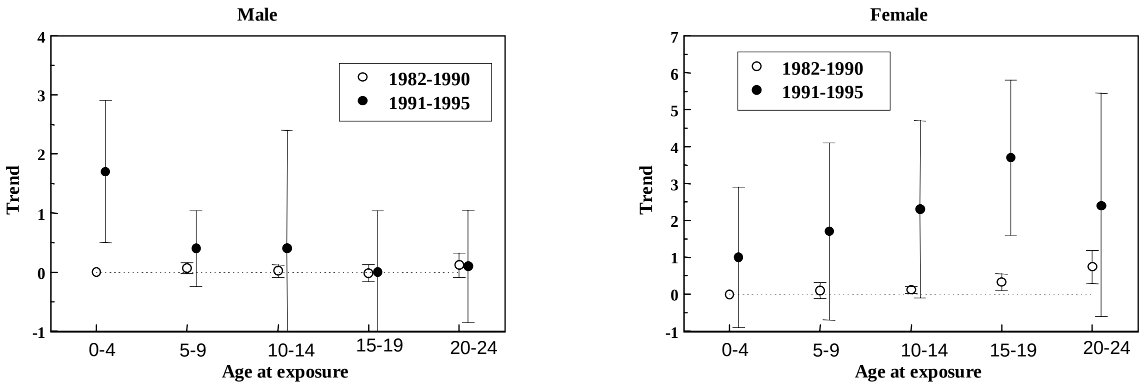

Fig. 14. Time trend in thyroid cancer incidence as a function of age at exposure.

Discussion and conclusion

In conclusion, let us formulate again the main results:

- the analysis of one age distribution of thyroid cancer cases based on Russian statistics and major foreign cancer registries shows that in eco-epidemiological study data of thyroid cancer incidence for the entire Russia can be taken as “control” in the age range 0-30 years;

- it has been established that SIR of thyroid cancer incidence in Bryansk, Tula and Orel regions in relation to “control” is characterized by statistically significant growth since 1991 on completion of the latent period;

- there is a major change in the age structure of incidence since 1991 due to the increase in thyroid cancer incidence in children and adolescents;

- the highest risk of developing thyroid cancer has been found in children up to 4 years at exposure (for them the risk is 6-10 times higher than that for adults);

- the risk for children born prior to the Chernobyl accident is in good agreement with the age dependence of thyroid doses from incorporated ^{131}I;

- the screening effect with the coefficient 1.6 has been established for thyroid cancer;

- no thyroid cancers were detected in children born after the Chernobyl accident.

Thus, the eco-epidemiological analysis of thyroid cancer incidence in the territories of Russia significantly contaminated after the Chernobyl accident indicates convincingly the radiation nature of the detected cancers in children and adolescents. At the same time, some important problems remain unresolved related to estimation of radiation doses and their uncertainties, determination of dose dependence in induction of thyroid cancers, influence of factors modifying radiation effects (iodine endemia, genetic predisposition).

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