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# Thyroid cancer overdiagnosis revisited

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ABSTRACT

*Background:* Evidence has accumulated showing that an increase in thyroid cancer incidence reflects overdiagnosis of clinically unimportant lesions due to the rise in the use of neck ultrasonography. In the manuscript we examine the hypothesis that the rise in thyroid cancer incidence in Russia is largely caused by overdiagnosis.
*Materials and methods:* Incidence and mortality rates of thyroid cancer for Russia overall and its administrative regions were abstracted from the statistical database of the Ministry of Health of Russia. For incidence trends, we calculated the percentage change, linear regression coefficient and p-value. The calculation of excess cases was based on expected age-specific distributions assuming that the incidence of thyroid cancer increases exponentially with age, as predicted by the multistage model of carcinogenesis.
*Findings:* Over the study period (1989–2015) the age standardized incidence of thyroid cancer has tripled in Russian women and doubled in men. Strong support for the hypothesis that the increase in thyroid cancer incidence may be artificial is evident from age-specific incidence trends: increases in incidence in middle age but not in older ages, thereby altering the age curves from the expected exponential shape to an "inverted U" shape. The number of observed cases of thyroid cancer exceeded the expected number by 138, 325 or 70 % of all cases diagnosed with thyroid cancer. We attribute the excess cases to detection by ultrasonography clinically unimportant lesions. This is supported by a very high incidence –to-mortality ratio, low case fatality, high and growing prevalence of thyroid cancer.
*Conclusion:* Although there is an evidence that exposure to iodine 131 ($^{131}$I) is an important cause of the increase in incidence of thyroid cancer in high-risk populations, we have shown that this increase could largely be attributed to overdiagnosis associated with ultrasonography screening. Overdiagnosis is the only explanation of the increase in thyroid cancer incidence in low-risk regions.

## 1. Introduction

The incidence of thyroid cancer is increasing worldwide, while mortality rates are declining. This increase has been attributed to exposure to radiation and other environmental factors implicated in thyroid cancer risk [1,2]. Recently, however, evidence has accumulated that the increase in thyroid cancer incidence rates reflects overdiagnosis of clinically unimportant indolent lesions due to the rise in the use of high-resolution neck ultrasonography and fine-needle aspiration [3–6]. Even in purportedly high-risk populations exposed to iodine 131 ($^{131}$I), the increase in the incidence of thyroid cancer has been partly attributed to the implementation of screening programs [7].

It has been reported that, in the regions of Russia affected by the Chernobyl accident (Bryansk, Kaluga, Oryol and Tula), or located in the vicinity of Semipalatinsk nuclear testing site (Altay), ultrasonography screening has a considerable impact on the reported incidence of thyroid cancer [8,9]. This assumption needs an additional evidence which could be provided by the analysis of incidence and mortality of thyroid cancer in Russia overall and its 82 administrative regions, including purportedly high-risk populations.

The manuscript examines the hypothesis suggesting that the increase in incidence of thyroid cancer in Russia overall and its administrative regions including those affected by radiation largely reflects overdiagnosis of clinically unimportant indolent lesions due to the rise in the use of neck ultrasonography.

## 2. Materials and methods

Age-standardized to world standard population incidence and mortality rates per 100,000 population and age-specific incidence rates by

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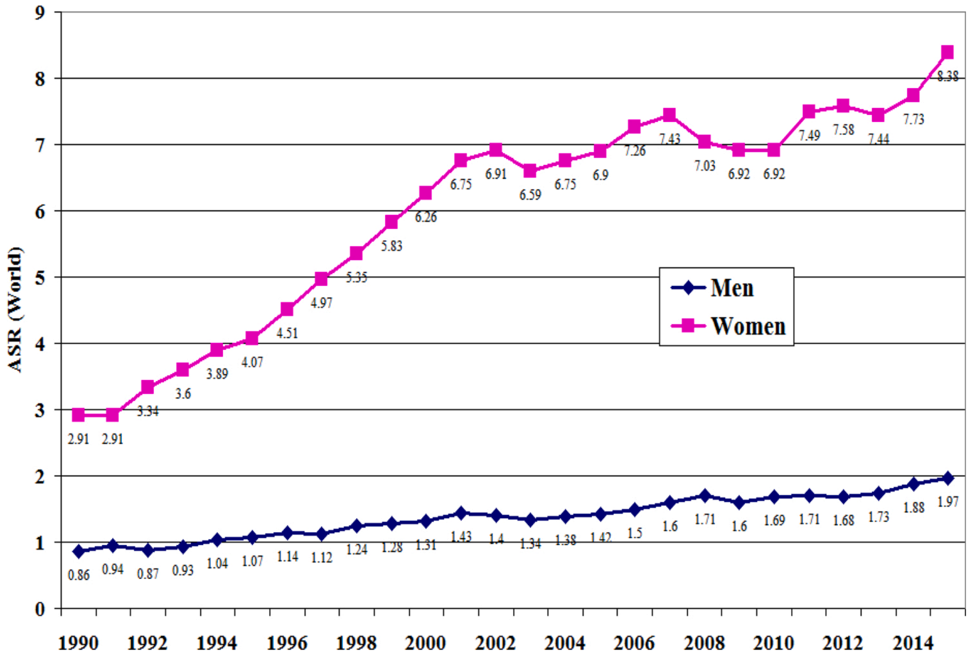


**Fig. 1.** Trends in age-standardized to world standard population incidence rates per 100,000 population of thyroid cancer in Russia.

sex of thyroid cancer were abstracted from the statistical database of the P.A. Herzen Research Institute of Oncology [10]. The Institute compiles and reports the data received from the Ministry of Health. The notification of newly diagnosed cancer cases is obligatory in Russia. Registration of all new cancer patients is the responsibility of regional cancer centers which serve defined catchment areas - administrative regions. All administrative regions and two cities (Moscow and St. Petersburg) report cancer incidence data to the Ministry of Health following the rules drawn up when the registration system was established, then amended in the following years to conform more closely to the international cancer registration format. The death certification covers 100 % of all deaths. The primary medical death certificate is issued by the physician or pathologist who performed the autopsy. Based on this, the regional statistical office (ZAGS) issues the death certificate on special letterhead stamped and duly signed by the statistical officer. These data is transferred to the Federal Statistics Agency (Rosstat) and the Ministry of Health.

Thyroid cancer incidence data for Russia overall have been available since 1989, while for the administrative regions since 1998. Mortality data have been available only since 2011. Ten regions were excluded from the analyses because of a limited number of cases. For incidence trends, we computed the percentage change, linear regression coefficient and p-value. Pearson correlation was used to study the relationship between the incidence of thyroid cancer and case fatality, the proportion of cases diagnosed at stage I and the prevalence of thyroid cancer. Procedures GLM and CORR of the SAS statistical package were used.

Maps were produced with the SAS gmap proc and the “mapsgfk. russia” base map (SAS (r) 9·4 - TS1M3). To illustrate the colors used on the maps, an estimate of the probability density for the rates was used as a legend, with the cut points for the different color classes indicated. This estimate was computed as the average of the normal densities with mean Ri and standard deviation Ei, where Ri and Ei are the incidence

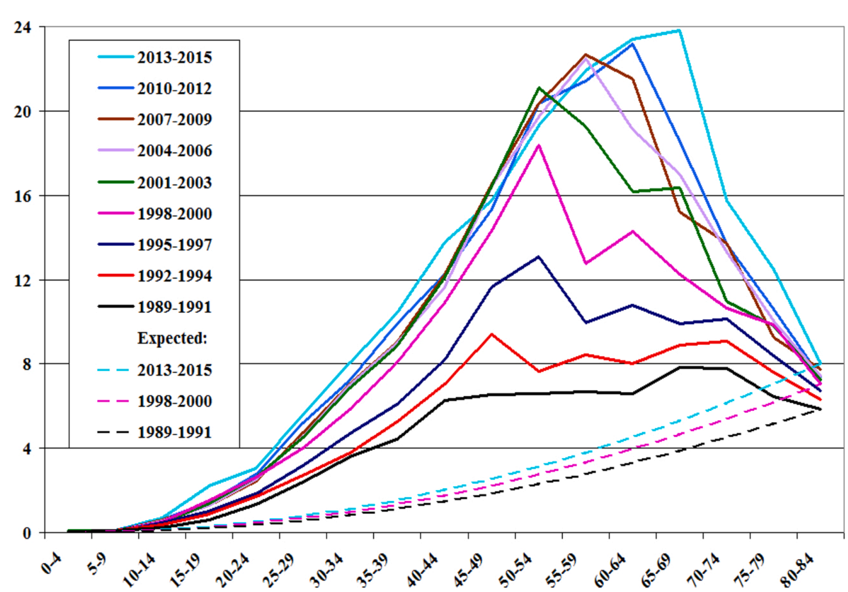


**Fig. 2.** Trends in age-specific incidence rates of thyroid cancer in Russia, women.

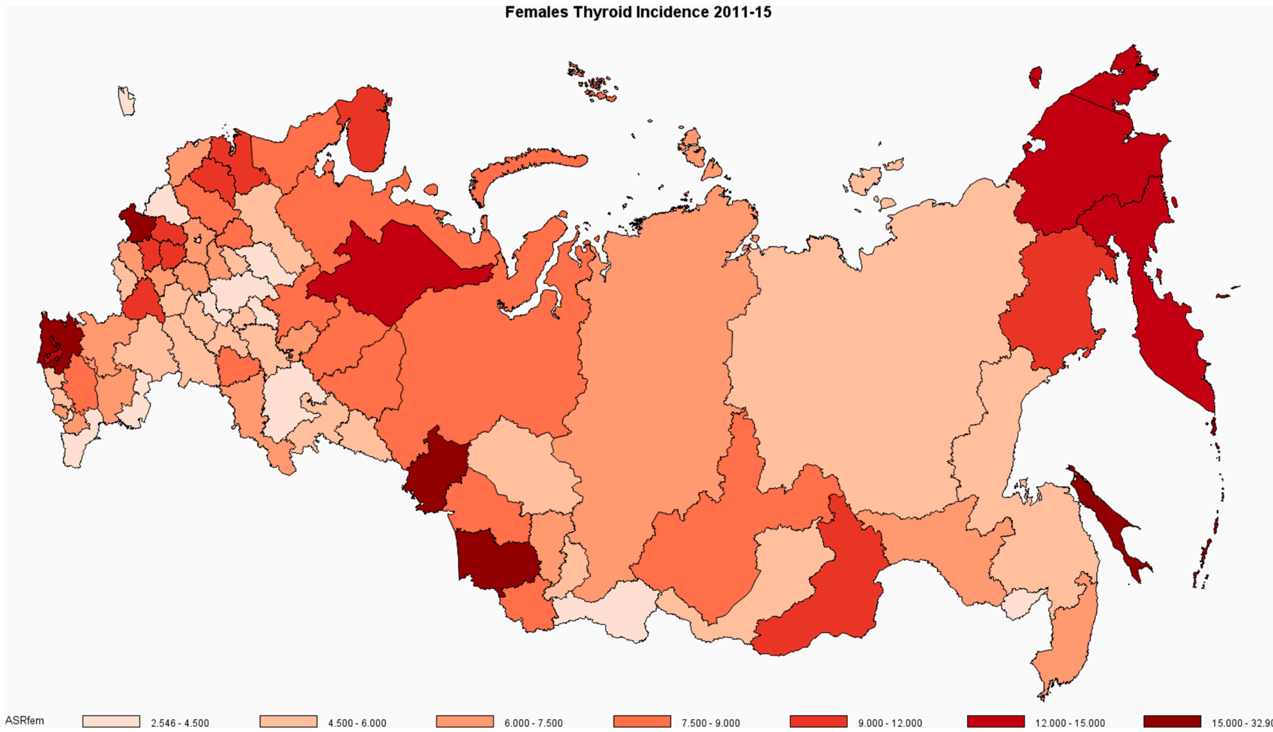


**Fig. 3.** Map of Russia, regional differences in incidence of thyroid cancer, women.

rate and the standard error for the region, respectively.

$$D = \frac{\sum N(Ri, s*Ei)}{n}$$

where n is 80 and s is a smooth factor (1 in the case of the male map, 2 for the female map) that allows the estimated density curve to be reasonably smooth. Cut points were chosen manually to ensure that they were reasonably placed in the range of variation of the rates, and they take the shape of the density into account.

Calculation of the excess cases of thyroid cancer was based on expected age-specific distributions according to the Armitage and Doll [11] multistage model of carcinogenesis for epithelial cancers: rate is proportional to $age^k$. The relevance of this model for thyroid cancer was confirmed by Vaccarella et al. [5] who showed that before introduction of ultrasonography in countries with long standing cancer registries thyroid cancer age specific incidence rates increased exponentially with age, consistent with the multistage model descried by Doll and Armitage [11].

The exponent k was estimated from the observed incidence with the assumption that, in the age group 80–84, the incidence was not affected by overdiagnosis. Expected distributions were estimated for each year from 1989 to 2015. We calculated excess cases (D) as the difference between the observed ($N_{obs}$) and expected ($N_{exp}$) number of cases for each age group:

$$D = N - N_{exp} = N * (1 - R_{exp}/R)$$

where Rexp and R - are the expected and observed rates, respectively. The overall excess for the period 1989–2015 is the sum of excess cases in each age group.

## 3. Results

Thyroid cancer incidence in Russia sharply increased over the past two and a half decades. The age standardized incidence rates per 100,000 population have nearly tripled in women and more than doubled in men (Fig. 1).

The age-specific incidence rates of thyroid cancer in women have also increased from 1989 to 2015 (Fig. 2). Dotted lines show expected age-specific rates for 1989–91, 1992–1994 and 2013–2015 based on the assumption that these curves have to have exponential shapes, as suggested by the model of multistage carcinogenesis for epithelial cancers. The sharpest progressive increases were seen in women and men (not shown) aged 50–64 years. There was practically no change in incidence above the age of 70.The number of observed incident cases (N) of thyroid cancer in women exceeded the expected number ($N_{exp}$) by 124, 882 and made up 74.2 % of the total number (168, 313) of thyroid cancer diagnosed in women in 1989−2015. The number of excess cases ($N-N_{exp}$) of thyroid cancer in men was 13, 443 or 44.4 % of all 30 306 thyroid cancers diagnosed in men. Thus the total number of excess or over-diagnosed cases in women and men was 138, 325 or 70 % out of 198,619 reported cases of thyroid cancer

The maps of thyroid cancer incidence (2011–2015) in women (Fig. 3) and men (Fig. A1) show pronounced regional variations, including sharp differences between geographically adjacent regions. Fig. A2 is a map of Russia with the names and codes of the administrative and territorial units that presumably will help the readers to locate the regions and make the link with maps on the Figs. 3 & A1 .

For women, the difference between the highest and lowest rates was 12-fold (Table 1); for men, this difference was 9.4-fold (Table A1). Very high incidence rates in both women and men were registered in the purportedly high-risk populations in the areas affected by the Chernobyl nuclear accident, such as Bryansk and the Altai, the region located in the vicinity of the former Soviet nuclear testing site in Semipalatinsk. Incidence was also high in some other areas geographically distant from them and from each other, for example, Krasnodar and Sakhalin. The variations in mortality rates from thyroid cancer between the regions were smaller, 5-fold in women and 4-fold in men.

The incidence-to-mortality ratio (I/M) for Russia as a whole is 15·5 for women and 5·9 for men (Table 1). However its size depends on age. Table 2 shows ratios of numbers of incidence cases (IC) to number of death (D) in different age groups. It is extremely high in young women, aged 25−29 (361) and 30−34 (687). Merits attention the observation that there was not a single death from thyroid cancer in women aged

**Table 1**
Incidence and mortality of thyroid cancer in Russia, women.

| Region | Mean 1998−2002 | Incidence[a] 2011−15 | Number of cases 2011−15 | Incidence[a] change (%) | Regression coefficient | P – value | Mortality[b] 2011−15 | I/M ratio 2011−15 |
|---|---|---|---|---|---|---|---|---|
| Russia | 6·22 | 7·72 | 43059 | 24·2 | 0·117 | <0·001 | 0·44 | 17·40 |
| *Central* | | | | | | | | |
| Belgorod | 6·12 | 5·95 | 350 | −2·8 | −0·009 | 0·854 | 0·48 | 12·34 |
| Bryansk | 17·52 | 32·90 | 1526 | 87·8 | 1·069 | <0·001 | 0·35 | 93·47 |
| Ivanovo | 5·59 | 4·83 | 228 | −13·6 | −0·026 | 0·571 | 0·28 | 17·11 |
| Kaluga | 5·20 | 11·72 | 443 | 125·2 | 0·488 | <0·001 | 0·42 | 27·64 |
| Kostroma | 2·19 | 3·38 | 92 | 54·5 | 0·091 | 0·089 | 0·50 | 6·82 |
| Kursk | 5·91 | 7·11 | 315 | 20·4 | 0·091 | 0·142 | 0·36 | 19·76 |
| Lipetsk | 4·67 | 7·46 | 343 | 59·9 | 0·199 | 0·002 | 0·50 | 14·81 |
| Moscow city | 5·17 | 5·99 | 2934 | 15·8 | 0·083 | 0·006 | 0·39 | 15·28 |
| Moscow region | 3·90 | 6·28 | 1773 | 61·1 | 0·198 | <0·001 | 0·48 | 13·19 |
| Oryol | 12·37 | 11·21 | 336 | −9·4 | −0·118 | 0·521 | 0·51 | 21·98 |
| Ryazan | 6·50 | 6·42 | 294 | −1·3 | −0·012 | 0·852 | 0·44 | 14·65 |
| Smolensk | 2·38 | 3·32 | 121 | 39·4 | 0·064 | 0·017 | 0·36 | 9·34 |
| Tambov | 8·09 | 5·97 | 250 | −26·3 | −0·157 | 0·051 | 0·40 | 14·92 |
| Tula | 6·11 | 9·62 | 600 | 57·6 | 0·290 | <0·001 | 0·51 | 18·94 |
| Tver | 9·42 | 7·83 | 435 | −16·9 | −0·136 | 0·277 | 0·43 | 18·39 |
| Vladimir | 1·94 | 6·17 | 366 | 218·5 | 0·308 | <0·001 | 0·70 | 8·79 |
| Voronezh | 7·61 | 10·69 | 979 | 40·5 | 0·271 | <0·001 | 0·32 | 33·83 |
| Yaroslavl | 5·62 | 8·00 | 425 | 42·4 | 0·208 | <0·001 | 0·61 | 13·20 |
| *North-West* | | | | | | | | |
| Arkhangelsk | 4·56 | 7·79 | 360 | 70·9 | 0·251 | <0·001 | 0·34 | 22·92 |
| Kaliningrad | 4·49 | 3·41 | 124 | −23·9 | −0·078 | 0·018 | 0·42 | 8·21 |
| Karelia | 7·02 | 8·88 | 230 | 26·6 | 0·125 | 0·236 | 0·43 | 20·56 |
| Komi | 3·87 | 12·24 | 406 | 215·9 | 0·636 | <0·001 | 0·41 | 29·70 |
| Leningrad region | 2·67 | 9·72 | 723 | 263·7 | 0·525 | <0·001 | 0·53 | 18·27 |
| Murmansk | 4·95 | 10·55 | 317 | 113·1 | 0·442 | <0·001 | 0·41 | 25·60 |
| Novgorod | 6·43 | 11·24 | 281 | 74·7 | 0·344 | 0·014 | 0·31 | 36·73 |
| Pskov | 4·04 | 6·38 | 171 | 57·9 | 0·176 | 0·012 | 0·61 | 10·39 |
| St-Petersburg city | 3·52 | 8·57 | 1824 | 143·3 | 0·381 | <0·001 | 0·47 | 18·08 |
| Vologda | 3·43 | 5·60 | 263 | 63·2 | 0·188 | 0·003 | 0·45 | 12·33 |
| *South* | | | | | | | | |
| Astrakhan | 2·64 | 2·80 | 112 | 6·3 | −0·013 | 0·778 | 0·38 | 7·46 |
| Kalmykia | 7·90 | 6·16 | 65 | −22·1 | −0·087 | 0·607 | 0·68 | 9·05 |
| Krasnodar | 20·81 | 16·77 | 3363 | −19·4 | −0·323 | 0·013 | 0·36 | 46·85 |
| Rostov | 7·21 | 6·49 | 1073 | −10·0 | −0·046 | 0·157 | 0·49 | 13·19 |
| Volgograd | 3·63 | 5·22 | 548 | 43·5 | 0·149 | 0·002 | 0·45 | 11·54 |
| *North-Caucasus* | | | | | | | | |
| Adygeya | 7·71 | 14·03 | 219 | 82·0 | 0·445 | 0·032 | 1·04 | 13·51 |
| Kabardino-Balkaria | 3·83 | 5·52 | 162 | 44·0 | 0·132 | 0·010 | 0·60 | 9·14 |
| Karachaevo-Cherkesia | 3·13 | 4·59 | 78 | 47·0 | 0·122 | 0·263 | 0·49 | 9·34 |
| North Osetia | 2·48 | 6·96 | 170 | 180·4 | 0·319 | <0·001 | 0·34 | 20·59 |
| Stavropol | 7·80 | 8·35 | 870 | 7·1 | 0·050 | 0·712 | 0·50 | 16·58 |
| *Volga* | | | | | | | | |
| Bashkortostan | 3·08 | 3·73 | 570 | 21·3 | 0·051 | 0·071 | 0·30 | 12·35 |
| Chuvashia | 4·31 | 4·95 | 232 | 14·9 | 0·058 | 0·328 | 0·27 | 18·35 |
| Kirov | 4·39 | 8·25 | 439 | 88·0 | 0·332 | <0·001 | 0·32 | 25·79 |
| Mordovia | 3·36 | 3·92 | 129 | 16·7 | 0·044 | 0·390 | 0·22 | 17·50 |
| Nizhnij Novgorod | 2·03 | 4·42 | 599 | 118·2 | 0·188 | <0·001 | 0·43 | 10·24 |
| Orenburg | 4·00 | 7·45 | 566 | 86·3 | 0·255 | <0·001 | 0·47 | 15·85 |
| Penza | 4·40 | 5·82 | 327 | 32·3 | 0·108 | 0·007 | 0·52 | 11·11 |
| Perm | 4·02 | 8·20 | 809 | 103·7 | 0·328 | <0·001 | 0·40 | 20·50 |
| Samara | 4·00 | 8·74 | 1168 | 118·2 | 0·362 | <0·001 | 0·37 | 23·87 |
| Saratov | 11·08 | 5·27 | 530 | −52·5 | −0·485 | <0·001 | 0·40 | 13·17 |
| Tatarstan | 3·23 | 5·57 | 833 | 72·4 | 0·196 | <0·001 | 0·44 | 12·54 |
| Udmurtia | 5·12 | 6·73 | 399 | 31·6 | 0·084 | 0·135 | 0·34 | 19·57 |
| Ulyanovsk | 4·87 | 4·82 | 236 | −0·9 | −0·014 | 0·805 | 0·39 | 12·31 |
| *Ural* | | | | | | | | |
| Chelyabinsk | 5·29 | 5·04 | 689 | −4·8 | −0·025 | 0·415 | 0·45 | 11·30 |
| Kurgan | 4·85 | 5·97 | 212 | 22·9 | 0·058 | 0·123 | 0·70 | 8·57 |
| Sverdlovsk | 7·23 | 7·98 | 1307 | 10·4 | 0·039 | 0·453 | 0·29 | 27·50 |
| Tyumen | 9·92 | 9·88 | 499 | −0·4 | 0·055 | 0·645 | 0·26 | 37·41 |
| *Siberia* | | | | | | | | |

(*continued on next page*)

Table 1 (*continued*)

| Region | Mean 1998–2002 | Incidence[a] 2011–15 | Number of cases 2011–15 | Incidence[a] change (%) | Regression coefficient | P – value | Mortality[b] 2011–15 | I/M ratio 2011–15 |
|---|---|---|---|---|---|---|---|---|
| Altay | 23·05 | 21·85 | 2014 | −5·2 | −0·129 | 0·449 | 0·42 | 51·54 |
| Buryatia | 3·63 | 4·57 | 154 | 25·8 | 0·055 | 0·362 | 0·69 | 6·64 |
| Irkutsk | 4·44 | 8·80 | 821 | 98·2 | 0·303 | 0·001 | 0·51 | 17·32 |
| Khakasia | 1·10 | 4·96 | 105 | 352·6 | 0·332 | <0·001 | 0·35 | 14·09 |
| Kemerovo | 9·03 | 7·35 | 787 | −18·7 | −0·162 | 0·006 | 0·40 | 18·46 |
| Krasnoyarsk | 4·16 | 7·20 | 794 | 73·0 | 0·234 | <0·001 | 0·59 | 12·21 |
| Novosibirsk | 5·62 | 8·42 | 899 | 49·8 | 0·219 | <0·001 | 0·66 | 12·84 |
| Omsk | 11·59 | 15·09 | 1095 | 30·2 | 0·305 | <0·001 | 0·38 | 39·31 |
| Tomsk | 9·65 | 5·33 | 222 | −44·7 | −0·319 | <0·001 | 0·59 | 8·98 |
| Zabaikalie | 8·78 | 9·14 | 338 | 4·1 | 0·035 | 0·682 | 0·53 | 17·11 |
| *Far-East* | | | | | | | | |
| Amur | 3·56 | 6·61 | 208 | 85·7 | 0·210 | <0·001 | 0·44 | 14·95 |
| Kamchatka | 7·78 | 12·97 | 154 | 66·7 | 0·411 | 0·002 | 0·50 | 25·73 |
| Khabarovsk | 3·46 | 5·51 | 287 | 59·4 | 0·152 | 0·004 | 0·51 | 10·85 |
| Primorie | 2·87 | 6·59 | 492 | 129·3 | 0·295 | 0·005 | 0·52 | 12·77 |
| Sakha (Yakutia) | 6·09 | 5·26 | 158 | −13·7 | −0·079 | 0·204 | 0·30 | 17·52 |
| Sakhalin | 17·32 | 16·94 | 312 | −2·2 | 0·034 | 0·886 | 0·47 | 36·20 |
| Mean value | 6·08 | 7·95 | 580·57 | 51·86 | 0·14 | 0·170 | 0·45 | 18·84 |
| Maximum | 23·05 | 32·90 | 3363·00 | 352·55 | 1·07 | 0·886 | 1·04 | 93·47 |
| Minimum | 1·10 | 2·80 | 65·00 | −52·47 | −0·49 | 0·001 | 0·22 | 6·64 |

[a] Age-standardized to world standard population incidence rates per 100,000 population.
[b] Age-standardized to world standard population mortality rates per 100,000 population.

**Table 2**
The ratio of number of incident cases of thyroid cancer to death from thyroid cancer by age in Russia. (2018).

| Age | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | N of incident cases (IC) | N of death (D) | IC/D | N of incident cases (IC) | N of death (D) | IC/D |
| All ages | 11101 | 721 | 15 | 2149 | 360 | 6 |
| 0−14 | 33 | 0 | – | 16 | 0 | – |
| 15−19 | 98 | 0 | – | 40 | 1 | 40 |
| 20−24 | 160 | 0 | – | 36 | 2 | 18 |
| 25−29 | 361 | 1 | 361 | 67 | 3 | 22 |
| 30−34 | 687 | 1 | 687 | 120 | 2 | 60 |
| 35−39 | 789 | 6 | 132 | 174 | 6 | 29 |
| 40−44 | 900 | 11 | 82 | 192 | 4 | 48 |
| 45−49 | 990 | 13 | 76 | 218 | 7 | 31 |
| 50−54 | 1136 | 22 | 52 | 223 | 34 | 7 |
| 55−59 | 1653 | 45 | 37 | 279 | 47 | 6 |
| 60−64 | 1582 | 73 | 22 | 305 | 58 | 5 |

0–25, while the registered number of incident cases in this age group was 291. It was one death from thyroid cancer in each of 25−29 and 30−34 age groups, while the number incident cases in these age groups was 361 and 687, respectively. In men these ratios are less, ranking from high (60) in age group 30−34 to low (5) in men aged 60−64 years.

It is a significant difference in the incidence-to-mortality ratio between regions. In women, it varied from 93.5 in Bryansk, 51.5 in Altai down to 6.8 in Kursk and 7.5 in Astrakhan (Table 1). The variation in the incidence-to-mortality ratio was lower in men, from relatively high in Murmansk (18.3) to low (2.0) in Voronezh (Table A1). There was also a marked difference between regions in case fatality, which varied in women from 1.1 % in the highest incidence region, Bryansk, to 14 % in a low-incidence region, Astrakhan. Incidence and case-fatality rates strongly correlated with one another (correlation coefficient = 0.67, $p < 0.0001$). In men, the variation in case fatality was less: the lowest (7.5 %) in Bryansk, the highest in Astrakhan (48 %), with a significant correlation between these two rates (correlation coefficient = 0.56, $p > 0.0001$).

The proportion of thyroid cancer diagnosed at stage I (tumor size $\leq 2$ cm at its widest diameter and limited to the thyroid) overall in Russia was 52.4 % for both sexes combined. It varied between regions from very high, up to 80 %, in high-incidence regions to 14 % in low-incidence regions. There was a statistically significant correlation between thyroid cancer incidence in 72 administrative regions and the proportion of thyroid cancer diagnosed at stage I for women and men combined (correlation coefficient = 0.67, $p < 0.0001$). As expected, the prevalence of thyroid cancer also varied markedly between regions, being high in areas known to be at high risk and low in low-risk areas with highly significant correlation between these 2 variables (correlation coefficient = 0.91; $p < 0.0001$). The highest prevalence of thyroid cancer is seen in Bryansk (401/100,000), followed by Altai (304/100,000 population). Prevalence rates were high in other purportedly high-risk regions: Oryol (181/100,000), Kaluga (150/100,000), Tula (145/100,000). In other areas, prevalence rates were low in order of 45–52/100,000. Between 2005 and 2015, the prevalence of thyroid cancer increased in Russia as a whole, from 62 to 101 per 100,000 population. There were substantial increases in high-risk regions: from 200/100,000 to 401/100,000 in the Bryansk oblast and from 190/100000 to 304/100,000 in Altai.

Thyroid cancer incidence rates in women increased in 54 of 72 regions included in the analysis. The increase was statistically significant ($p < 0.05$) in 43 of them. The incidence more than doubled in 12 administrative regions geographically distant from each other (Table 1). In men, thyroid cancer increased in 62 administrative regions. In 30 of them, the increase was statistically significant (Table A1).

## 4. Discussion

This is the first study to document the overdiagnosis of thyroid cancer in Russia. Before discussing our findings in detail, we need to consider the Chernobyl nuclear power plant accident in 1986, which resulted in the contamination of large areas in Ukraine, Belarus and the Russian Federation with radionuclides (chiefly $^{131}I$) [12,13]. In Russia, the regions thought to be strongly affected by radiation include Bryansk, Kaluga, Oryol and Tula. Several studies have reported the increased incidence of thyroid cancer in these regions among people exposed to $^{131}I$ in childhood and adolescence [12,13]. The Altai region is another purportedly high-risk area for thyroid cancer because of its proximity to Semipalatinsk (Kazakhstan), the former Soviet nuclear test site [9].

Our study demonstrated a very high incidence of thyroid cancer, particularly in women, in Bryansk, one of the regions affected by the Chernobyl accident, with a significant increase in rates between circa

2000 and circa 2013 in both men and women. The population of the Altai region had the second highest rates of thyroid cancer in Russia.

Based on the existing evidence, we conclude that exposure to $^{131}$I was an important cause of the increase in the incidence of thyroid cancer. The follow-up of residents of the contaminated territories demonstrated an increased risk of thyroid cancer among members of the cohort exposed to $^{131}$I in childhood and adolescence (0–17 years of age at the time of the Chernobyl accident), with a strong association between the risk and the estimated individual dose of $^{131}$I absorbed by the thyroid gland [14–16]. However, we demonstrated that the reported high incidence of thyroid cancer was largely due to detection by ultrasonography screening clinically unimportant indolent lesions. This conclusion is strongly supported by a very high incidence-to-mortality ratio, very low case fatality, very high and growing prevalence of thyroid cancer.

It was estimated that only approximately 40 % of detected thyroid cancer cases can be attributed to radiation [8,12]. Thus, the other 60 % of cases represent background incidence and are spontaneous carcinomas including small, latent, clinically indolent lesions discovered at screening. Among histologically confirmed cases of thyroid cancer, the vast majority (94–95 %) of cases were papillary carcinoma.

The substantial growth of thyroid cancer incidence was observed during the first 4 years (1987–1990) after accident. Only explanation of this increase is overdiagnosis due to the introduction of ultrasonography screening, inasmuch as thyroid cancer occurs at least 5–10 years after exposure to radiation [8,17,18]. The screening effect was also demonstrated in emergency workers, among whom the observed numbers of thyroid cancer were 2.6 times higher than expected based on pre-accident statistics [8,17,19].

The ultrasound screening in the regions contaminated by $^{131}$I was initiated in 1987, immediately after Chernobyl accident [8]. Formal thyroid cancer screening program was also set up in 1992 in Altai region considered as a high risk area due to vicinity to Semipalatinsk nuclear testing site [9]. The "radiation phobia" contributed to the spread of the neck ultrasonography in Russia outside the purportedly high risk areas. This trend was largely supported by representatives of medical profession who widely recommended neck ultrasonography for early diagnosis [20].

However we do not have the exact quantitative information on the regional patterns of the use of neck ultrasonography.

We report that the increase in incidence of thyroid cancer in the Altai region, considered to be at high risk because of its proximity to the former Soviet nuclear testing site in Semipalatinsk, was likewise caused by intensive opportunistic screening, which resulted in overdiagnosis. Lazarev et al. [9] demonstrated an association between the absorbed radiation doses and the incidence of thyroid cancer in the Altai region. The introduction of screening programs affected the detection rate of thyroid cancer, which increased from 8.7%–20.3% between 1992 and 1999. According to the authors, "improvement in diagnostic methods resulted in the detection of papillary minimal cancers measuring 3–5 mm". The proportion of such minimal lesions among all thyroid gland cancers reached 52 % in 1998. The increase in incidence of thyroid cancer was not accompanied by an increase in mortality, which remained stable at the rate of 1 per 100,000 population. Between 1987 and 2002, the prevalence of thyroid cancer in Altai increased 5.6–fold, from 23 to 131 per 100,000 population.

Thus, although exposure to radiation (specifically, $^{131}$I) has a major impact on the reported incidence of thyroid cancer in purportedly high-risk areas, ultrasonography screening is an additional important factor affecting incidence via the detection of small, latent, asymptomatic, indolent lesions in the thyroid gland that would never manifest themselves clinically if not detected by modern high-resolution techniques such as ultrasonography and fine-needle biopsy.

We have shown that the incidence of thyroid cancer was also high in several regions geographically distant from the areas affected by the Chernobyl accident or the Semipalatinsk nuclear testing site, as well as from each other. In most of these regions, the strong and significant increases in the rates between 2000 and 2013, particularly in women, can hardly be explained by the effect of any known or suspected risk factors [1,2]. The widespread introduction of neck ultrasonography may, therefore, be the only explanation for the high and increasing rates of thyroid cancer in regions that are not affected by radiation risk.

Strong support for the hypothesis that the increase in thyroid cancer incidence may be artificial is evident from age-specific incidence trends: sharp increases in incidence in middle age but not in older ages, thereby altering the age curves from the expected exponential shape, as predicted by the Armitage and Doll's [11] multistage model of carcinogenesis for epithelial cancers to an "inverted U" shape. The calculation of excess cases (number of overdiagnosed cases) based on expected exponential patterns of age-specific curves for each year showed that, from 1989 to 2015 the number of excess cases of thyroid cancer in women was 124,882 and 13,443 in men, or a total of 138,325. We attributed the excess cases beyond the expected numbers to the introduction of sensitive diagnostic techniques, which had a substantial impact on the reported incidence of thyroid cancer. This observation closely corresponds to the results of the analyses of thyroid cancer incidence trends by age in 12 developed countries by Vaccarella et al. [3] who showed that more than 550,000 women and men may have been overdiagnosed with thyroid cancer during two recent decades in the countries studied. Recently massive overdiagnosis of thyroid cancer has been demonstrated for Belorus the country also affected by Chernobyl accident. It has been estimated that 4352 cases or 90.6 % of all thyroid cancers diagnosed in this country in 2008–2012 were overdiagnosed [21].

The available evidence suggests that new diagnostic and screening practices have a large impact internationally on thyroid cancer rates, enabling the detection of clinically unimportant, indolent, latent tumors [22].

The obtained evidence will help to overcome the deep-rooted belief that the early detection of cancer is always beneficial and screening is bound to be effective and will discourage the performance of neck ultrasonography, which is still widely used in many countries.

## 5. Strengths and limitations

This study contributes to the existing literature by providing first-hand evidence on the overdiagnosis of thyroid cancer in Russia, using Russian nationally representative population-based data, covering all administrative regions over the past 26 years. Nevertheless, several limitations should be considered when interpreting our findings.

- One of the most important limitations of the study is that the quality of registration varies between administrative regions of Russia and these impacts the comparisons of the rates between regions. The very low rates of thyroid cancer in some registries could be explained by under registration of thyroid cancer.
- The information on histological types of thyroid cancer is available only for high risk regions (Bryansk and Altai) while for the rest of administrative regions and Russia as a whole such information is not available.
- Along with formal ultrasonography screening of thyroid cancer introduced in high risk regions (Bryansk and Altai), the use of neck ultrasonography dramatically increased in the country in general. However we do not have the exact quantitative information on the regional patterns of the ultrasonography use.

## 6. Conclusions

We provide strong quantitative evidence of thyroid cancer overdiagnosis in Russia: during last three decades 138,325 men and women were overdiagnosed with thyroid cancer.

While exposure to $^{131}$I had an important impact on the increase of

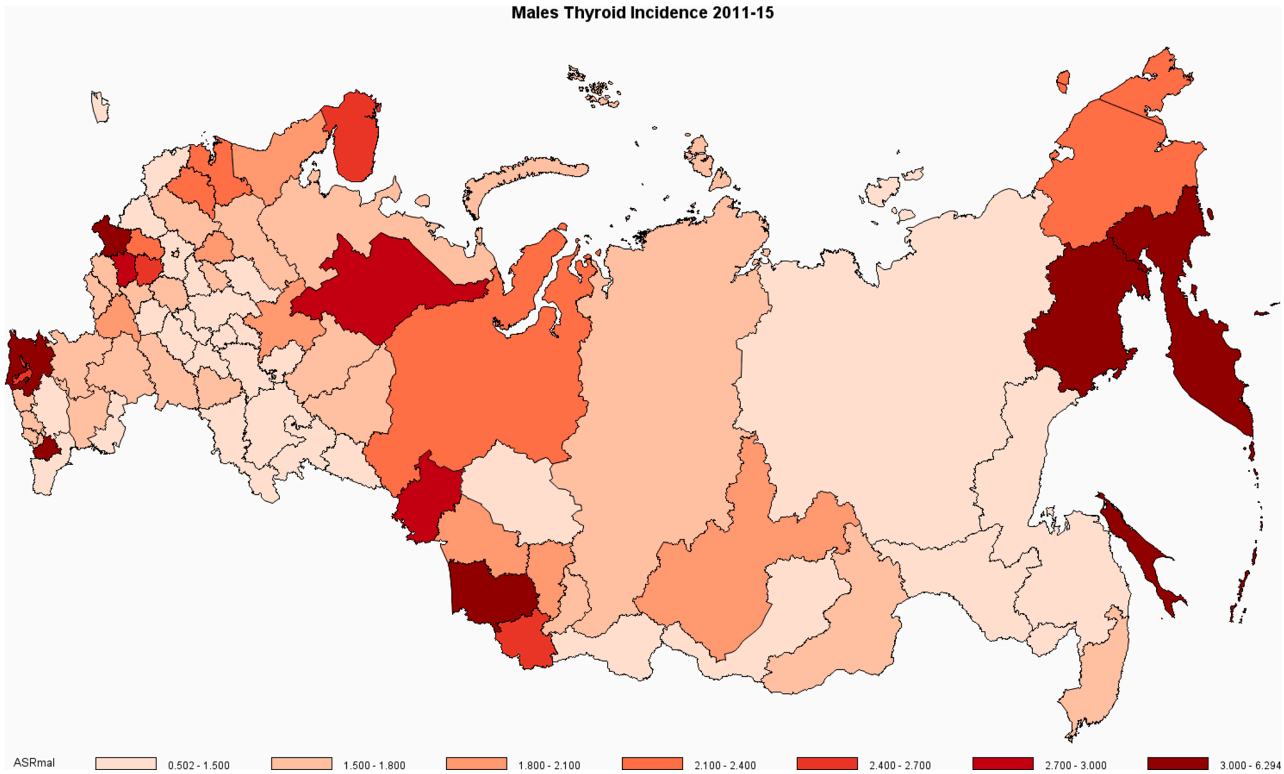


**Fig. A1.** Map of Russia, regional differences in thyroid cancer incidence, men.


**Fig. A2.** Map of Russia with the names and codes of the administrative units.

incidence in the regions affected by radiation, ultrasonography screening has contributed to this increase via detection of indolent clinically unimportant lesions.

Overdiagnosis is the only explanation of the increase in thyroid cancer incidence in low risk regions.

## Author contribution

David Zaridze: study concept, study design, data interpretation, manuscript preparation, manuscript editing, review.

Dimitry Maximovitch: data acquisition, quality control, interpretation, statistical analysis.

Michel Smans: design of the maps and interpretation.

Ivan Stilidi: supervision, data administration, manuscript review.

## Declaration of Competing Interest

The authors do not have any actual or potential conflict of interest including any financial, personal or other to be declared.

**Table A1**
Incidence and mortality from thyroid cancer in Russia and its 72 regions, men.

| Region | Mean 1998–2002 | Incidence[a] 2011–15 | Number of cases 2011–15 | Incidence[a] Change (%) | Regression coefficient | P –value | Mortality[b] 2011–15 | I/M ratio 2011–15 |
|---|---|---|---|---|---|---|---|---|
| Russia | 1·33 | 1·79 | 7803 | 34·7 | 0·038 | <0·001 | 0·36 | 4·96 |
| *Central* | | | | | | | | |
| Belgorod | 1·45 | 1·61 | 80 | 11·2 | 0·022 | 0·318 | 0·52 | 3·07 |
| Bryansk | 4·16 | 6·29 | 230 | 51·4 | 0·159 | <0·001 | 0·47 | 13·33 |
| Ivanovo | 1·39 | 1·50 | 50 | 8·1 | 0·016 | 0·448 | 0·59 | 2·53 |
| Kaluga | 1·21 | 2·28 | 64 | 89·1 | 0·077 | 0·040 | 0·27 | 8·59 |
| Kostroma | 0·87 | 0·82 | 19 | −5·5 | −0·004 | 0·770 | 0·19 | 4·42 |
| Kursk | 1·18 | 1·71 | 56 | 44·7 | 0·056 | 0·093 | 0·43 | 4·01 |
| Lipetsk | 1·30 | 1·60 | 61 | 22·5 | 0·025 | 0·191 | 0·26 | 6·10 |
| Moscow city | 1·44 | 1·72 | 649 | 19·4 | 0·028 | 0·002 | 0·33 | 5·16 |
| Moscow region | 0·99 | 1·38 | 306 | 40·2 | 0·035 | 0·001 | 0·31 | 4·40 |
| Oryol | 2·87 | 2·70 | 63 | −5·9 | −0·010 | 0·823 | 0·43 | 6·34 |
| Ryazan | 1·52 | 1·59 | 56 | 4·7 | 0·006 | 0·778 | 0·40 | 3·97 |
| Smolensk | 0·90 | 0·91 | 26 | 2·0 | 0·001 | 0·935 | 0·34 | 2·72 |
| Tambov | 0·93 | 1·20 | 41 | 29·1 | 0·019 | 0·243 | 0·22 | 5·50 |
| Tula | 1·47 | 2·53 | 123 | 72·4 | 0·073 | 0·010 | 0·30 | 8·54 |
| Tver | 1·43 | 1·77 | 76 | 23·6 | 0·038 | 0·075 | 0·25 | 7·13 |
| Vladimir | 0·84 | 1·10 | 48 | 30·5 | 0·027 | 0·151 | 0·55 | 2·01 |
| Voronezh | 1·46 | 1·98 | 150 | 36·1 | 0·043 | 0·020 | 0·28 | 7·08 |
| Yaroslavl | 1·19 | 1·99 | 74 | 68·0 | 0·078 | 0·001 | 0·40 | 5·03 |
| *North-West* | | | | | | | | |
| Arkhangelsk | 1·12 | 1·78 | 62 | 59·2 | 0·058 | 0·008 | 0·23 | 7·67 |
| Kaliningrad | 1·21 | 1·18 | 36 | −2·0 | 0·004 | 0·801 | 0·43 | 2·75 |
| Karelia | 1·08 | 1·94 | 35 | 79·1 | 0·052 | 0·149 | 0·38 | 5·10 |
| Komi | 1·44 | 2·90 | 73 | 102·0 | 0·108 | 0·007 | 0·43 | 6·68 |
| Leningrad region | 0·82 | 2·15 | 117 | 163·5 | 0·098 | <0·001 | 0·45 | 4·78 |
| Murmansk | 1·46 | 2·60 | 61 | 77·9 | 0·098 | 0·010 | 0·14 | 18·34 |
| Novgorod | 1·27 | 2·34 | 44 | 84·2 | 0·100 | 0·050 | 0·44 | 5·26 |
| Pskov | 1·09 | 0·76 | 16 | −30·3 | −0·040 | 0·099 | 0·12 | 6·44 |
| St-Petersburg city | 1·15 | 1·88 | 278 | 63·5 | 0·060 | 0·005 | 0·42 | 4·46 |
| Vologda | 1·33 | 1·56 | 55 | 17·5 | 0·023 | 0·306 | 0·37 | 4·23 |
| *South* | | | | | | | | |
| Adygeya | 2·01 | 2·65 | 37 | 31·9 | 0·033 | 0·397 | 0·14 | 18·39 |
| Astrakhan | 1·04 | 0·97 | 30 | −6·5 | 0·007 | 0·632 | 0·47 | 2·07 |
| Kalmykia | 0·78 | 1·63 | 15 | 109·5 | 0·082 | 0·150 | 0·41 | 3·95 |
| Krasnodar | 2·87 | 3·50 | 571 | 21·9 | 0·054 | 0·007 | 0·40 | 8·65 |
| Rostov | 1·78 | 1·70 | 228 | −4·4 | −0·005 | 0·809 | 0·44 | 3·90 |
| Volgograd | 1·23 | 1·63 | 129 | 32·6 | 0·032 | 0·050 | 0·34 | 4·76 |
| *North-Caucasus* | | | | | | | | |
| Dagestan | 0·96 | 0·97 | 69 | 1·3 | −0·001 | 0·970 | 0·32 | 3·05 |
| Kabardino-Balkaria | 1·28 | 1·58 | 36 | 23·2 | 0·021 | 0·480 | 0·33 | 4·73 |
| Karachaevo-Cherkesia | 0·85 | 1·58 | 22 | 86·3 | 0·076 | 0·066 | 0·28 | 5·56 |
| North Osetia | 0·89 | 1·55 | 31 | 74·4 | 0·041 | 0·106 | 0·43 | 3·59 |
| Stavropol | 1·27 | 1·43 | 128 | 13·1 | 0·013 | 0·517 | 0·39 | 3·69 |
| *Volga* | | | | | | | | |
| Bashkortostan | 0·93 | 0·66 | 80 | −29·0 | −0·017 | 0·058 | 0·25 | 2·62 |
| Chuvashia | 1·33 | 1·05 | 40 | −21·4 | −0·018 | 0·208 | 0·32 | 3·23 |
| Kirov | 1·03 | 1·87 | 79 | 81·0 | 0·067 | 0·006 | 0·37 | 5·01 |
| Mordovia | 1·00 | 1·17 | 31 | 16·8 | 0·022 | 0·467 | 0·26 | 4·48 |
| Nizhnij Novgorod | 0·80 | 1·04 | 109 | 29·8 | 0·020 | 0·061 | 0·31 | 3·35 |
| Orenburg | 1·48 | 1·40 | 84 | −5·4 | −0·014 | 0·503 | 0·36 | 3·84 |
| Penza | 1·02 | 1·29 | 57 | 25·8 | 0·014 | 0·432 | 0·46 | 2·77 |
| Perm | 1·02 | 1·52 | 117 | 49·4 | 0·043 | 0·019 | 0·23 | 6·51 |
| Samara | 1·11 | 1·80 | 181 | 62·3 | 0·052 | 0·003 | 0·37 | 4·81 |
| Saratov | 2·33 | 1·59 | 124 | −31·7 | −0·062 | 0·041 | 0·31 | 5·18 |
| Tatarstan | 0·89 | 1·42 | 162 | 60·0 | 0·043 | 0·006 | 0·32 | 4·42 |
| Udmurtia | 1·14 | 1·31 | 64 | 14·7 | 0·022 | 0·207 | 0·43 | 3·02 |
| Ulyanovsk | 1·18 | 1·50 | 60 | 26·6 | 0·032 | 0·051 | 0·40 | 3·74 |
| *Ural* | | | | | | | | |
| Chelyabinsk | 1·08 | 1·22 | 125 | 13·6 | 0·010 | 0·341 | 0·32 | 3·82 |
| Kurgan | 0·94 | 1·21 | 32 | 29·0 | 0·011 | 0·657 | 0·51 | 2·38 |
| Sverdlovsk | 1·22 | 1·61 | 206 | 31·6 | 0·026 | 0·124 | 0·32 | 4·96 |
| Tyumen | 1·68 | 2·77 | 108 | 65·2 | 0·088 | 0·002 | 0·24 | 11·73 |

(*continued on next page*)

**Table A1** (*continued*)

| Region | Mean 1998–2002 | Incidence[a] 2011–15 | Number of cases 2011–15 | Incidence[a] Change (%) | Regression coefficient | P –value | Mortality[b] 2011–15 | I/M ratio 2011–15 |
|---|---|---|---|---|---|---|---|---|
| *Siberia* | | | | | | | | |
| Altay | 2·49 | 5·27 | 399 | 111·9 | 0·216 | <0·001 | 0·51 | 10·38 |
| Buryatia | 0·97 | 1·25 | 31 | 28·3 | 0·012 | 0·492 | 0·52 | 2·41 |
| Irkutsk | 0·95 | 2·07 | 140 | 117·4 | 0·088 | <0·001 | 0·32 | 6·48 |
| Khakasia | 0·65 | 1·63 | 25 | 148·9 | 0·083 | 0·004 | 0·47 | 3·46 |
| Kemerovo | 1·59 | 1·92 | 155 | 20·6 | 0·029 | 0·099 | 0·38 | 5·10 |
| Krasnoyarsk | 0·79 | 1·54 | 130 | 95·4 | 0·064 | 0·004 | 0·36 | 4·34 |
| Novosibirsk | 1·12 | 2·00 | 166 | 79·4 | 0·068 | <0·001 | 0·41 | 4·91 |
| Omsk | 1·73 | 2·73 | 149 | 57·8 | 0·080 | 0·002 | 0·23 | 11·77 |
| Tomsk | 1·45 | 1·40 | 41 | −3·0 | −0·012 | 0·668 | 0·33 | 4·28 |
| Zabaikalie | 1·16 | 1·59 | 45 | 37·2 | 0·042 | 0·114 | 0·12 | 13·51 |
| *Far-East* | | | | | | | | |
| Amur | 0·70 | 1·34 | 34 | 90·1 | 0·054 | 0·040 | 0·80 | 1·68 |
| Kamchatka | 1·53 | 3·52 | 37 | 130·4 | 0·162 | <0·001 | 0·79 | 4·46 |
| Khabarovsk | 0·87 | 1·47 | 54 | 68·5 | 0·044 | 0·037 | 0·36 | 4·10 |
| Primorie | 0·75 | 1·76 | 108 | 136·5 | 0·081 | <0·001 | 0·53 | 3·33 |
| Sakha (Yakutia) | 1·37 | 1·43 | 37 | 4·8 | −0·008 | 0·727 | 0·26 | 5·60 |
| Sakhalin | 3·01 | 3·37 | 52 | 12·2 | 0·024 | 0·681 | 0·58 | 5·81 |
| Mean value | 1·32 | 1·83 | 104·26 | 42·97 | 0·04 | 0·230 | 0·37 | 5·49 |
| Maximum | 4·16 | 6·29 | 649·00 | 163·48 | 0·22 | 0·970 | 0·80 | 18·39 |
| Minimum | 0·65 | 0·66 | 15·00 | −31·71 | −0·06 | 0·001 | 0·12 | 1·68 |

[a] Age-standardized to world standard population incidence rates per 100,000 population.
[b] Age-standardized to world standard population mortality rates per 100,000 population.

## Appendix A

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