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Iodine Excretion in Regions of Ukraine Affected by the Chornobyl Accident: Experience of the Ukrainian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases

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Urinary iodine concentrations were measured in 11,926 subjects who are participants in the Ukrainian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases Following the Chornobyl Accident. Measurements were made in two time periods corresponding to the first and second thyroid screening cycles (1998-2000,2001-2009). These time periods fall before and after initiation of a government program to increase iodine sufficiency. Median urinary iodine concentrations did increase in the later time period compared to the earlier [47.5 µg/L, 95% confidence interval (CI) 46.5-48.9 µg/L versus 41,7 µg/L, 95% CI 40.4-42.5 µg/L], but levels remained in the mild-to-moderate iodine deficiency range as defined by the World Health Organization (WHO), indicating the need for further efforts at iodination. In both time periods, urinary iodine levels were found to vary by place of residence and were lower in rural compared to urban areas. Iodine status needs to be considered when evaluating risk of thyroid cancer and other thyroid diseases.

Introduction

THE NORTHERN TERRITORY OF UKRAINE, an area of long-standing moderate iodine deficiency, was affected by massive releases of radioactive fallout from the nuclear plant accident at Chomobyl (Chernobyl) on April 26, 1986. The population of the contaminated areas was exposed primarily to $^{13]}$I, which concentrates in the thyroid gland. Contaminated milk and other foods were the major sources of exposure in the post-accident period.

Striking increases in thyroid cancer among exposed children have since been described (1,2). The impact of iodine deficiency in conjunction with radiation exposure is still uncertain, in part because few studies have addressed the issue. Iodine is critical to the regulation of thyroid hormones (3), and iodine insufficiency may modify risk of thyroid cancer both by affecting uptake of radioiodines at the time of exposure and altering thyroid function following exposure. Experimental studies (4) indicate that iodine deficiency may be an important modifier of radiation-induced thyroid cancer risk. A recent ecologic study in the Bryansk region of the Russian Federation (5) and a large case-control study in Belarus (6) have both reported an inverse relationship between the excess relative risk of thyroid cancer and iodine levels. There is also evidence that thyroid cancer of the follicular and anaplastic types is more common in iodine-deficient areas (7). Ukraine has generally been an area of mild-to-moderate iodine deficiency (8).

The primary objective of the present report is to document levels of iodine in parts of Ukraine affected by Chomobyl fallout. Data are presented for two time periods, one before and one after Ukrainian governmental decrees in 2001 establishing mandatory programs to eliminate iodine deficiency by improving iodine intake. The study cohort of approximately 13,000 individuals, subjects in the Ukrainian-American Cohort Study of Thyroid Cancer and Other Thyroid Diseases, who have been followed in biennial screening examinations since 1998, contributed casual urine samples for measurement of urinary iodine excretion as a marker for iodine nutrition. We examined patterns of iodine nutrition by time period, place of residence, and urban/rural status, adjusting for age and gender, and evaluated questionnaire data on intake of foods and preparations with high concentrations of iodine.

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Materials and Methods

Details of the methods of both the Ukrainian study and a parallel study in Belarus have been published previously (9). In brief, the cohort in Ukraine consists of 13,243 subjects who at the time of the Chomobyi accident in 1986 were 0-18 years of age, had at least one direct measurement of thyroid radioactivity, and lived in Kyiv oblast (site of the Chomobyi Nuclear Power Station), or Zhytomyr or Chernihiv oblasts, the oblasts located on either side of Kyiv oblast.

Forty individuals who were not bom or were over 18 years of age at the time of the accident on April 26,1986, and 1,277 who did not have urinary iodine measurements were excluded, resulting in a sample of 11,926 for analysis of urinary iodine in the first screening cycle. In the second screening cycle, urine iodine data were available for 11,939 subjects,

Trie study protocol was approved by Institutional Review Boards in the United States and Ukraine. All subjects gave signed informed consent.

Screening began in 1998, and the first screening cycle was completed in 2000; the second screening cycle ran from 2001 to 2003. Screening examinations were performed at the Institute of Endocrinology and Metabolism (ΓEM) in Kyiv or by mobile teams mat traveled to the regions where the study subjects live. Approximately 25% of the examinations were performed at the Institute and 75% by the mobile teams.

Each screening examination includes a history and physical examination by an endocrinologist, and an ultrasound examination of the neck and thyroid gland by an ultrasonographer. At the time of the examination, a casual urine specimen is obtained for urinary iodine measurement.

The urine specimen was collected in a plastic container and an aliquot was transferred to a 3-ml test tube labeled with a barcode containing the subject's study number. Test tubes are sealed with a cap, stored in a refrigerator, and conveyed to the Urinary Iodine Laboratory at the IEM In Kyiv to be tested for iodine content. After receipt at the Institute, samples are stored at -18°C until analysis.

Urinary iodine content is measured using chloric acid digestion coupled to spectrophotometric detection of the Sandell-Kolthoff reaction (10,11) and expressed in μg/L. The analytic sensitivity of the assay iз 6 μg/L. Internal quality control is monitored using repeat measurements of two levels of pooled urine with the results plotted on Levey-Jennings charts for the detection of out-of-control runs. Any run with a control out of range is repeated. The laboratory also participates in periodic quality assurance programs, such as the Equip program carried out by CDC.

We examined urinary iodine excretion levels by time period (first and second cycle), place of residency (oblast, raion), and type of residency (urban or rural) at the time of examination. An oblast is an administrative subdivision similar in size to a state or province; a raion is similar in size to a county or district. Urban and rural populations were defined using the administrative and territorial divisions of Ukraine (12). According to these criteria, place of residence was classified as one of the following: city, large settlement with some urban features, large village, or village. In the analysis, residence In a city was considered 'urban'; all others were categorized as 'rural.'

At the time of urine collection, subjects were asked about their current use of iodine-containing vitamins and drugs, iodinated salt and foods rich in iodine, as well as Iodine preparations. These data were used to compare estimated iodine intake in Cycle 1 and Cycle 2.

As a context for evaluating urinary Iodine levels, WHO has established the following guidelines (13); adequate intake is defined as > = 100 μg/L. mild iodine deficiency as 50-99 μg/L, moderate iodine deficiency as 20-49 μg/L, and severe iodine deficiency as 0-19 μg/L.

The relationship between urinary iodine level and the selected predictive factors, adjusted for gender and age, was evaluated using fitted generalized linear regression models as implemented in PROC GLM (SAS version 8.0). The general regression model was as follows: LN (Iodine) - a + β*x + γ*age +δ*gender, where a is the Intercept; β, γ and δ are the estimated regression coefficients for the effect of factor x under consideration (place of residence or type of settlement), age, and gender, respectively. As a representative summary of urinary iodine concentrations, estimated means and medians, with 95% confidence intervals, were computed for a 20-year-old female; thus, the results for subgroups can be directly compared. The Cycle 2 median was compared with Cycle 1 using the mean of the difference between the natural logarithms of iodine concentration in Cycle 2 and Cycle 1 estimated from an analysis of variance (ANOVA) adjusting for within-person variability, age and gender. All tests were two-sided and p values less than 0.05 were considered significant.

Result*

The cohort consists of individuals who, at the time of the accident, were residents of Kyiv and Chernihiv cities as well as selected raions that have among the highest levels of radioactive contamination in Ukraine: Zhytomyr oblast (Narodychi and Ovruch raions), Chernihiv oblast (Chernihiv, Ripky, and Kozelets' raions), and Kyiv oblast (Poliss'ke and Ivankiv raions). The geographical distribution of cohort members at the time of the first screening (Fig. 1) indicates that a majority of the examined subjects were still living within 100 km of the Chomobyi plant. Males comprised 50.9% of the cohort. The mean age at first screening was 21.5 years, with a range of 12-32.5 years.

In the first screening cycle (Table 1), median urinary iodine excretion for the cohort as a whole was indicative of moderate iodine deficiency [41.7 μg/L, 95% confidence interval (CI) 40.4-42.5). None of the individual regions studied showed mean or median levels in the severely iodine deficient range, although at the individual level, 14% of the cohort had concentrations below 20 μg/L. The highest median urinary iodine concentrations were reported for the raions of Kyiv oblast (other than Ivankiv and Kyiv city) (54 μg/L), and for Chernihiv city (51.9 μg/L) and Kyiv city (47.5 μg/L). The lowest levels of urinary iodine excretion were reported in Ovruch and Narodychi raions, where the median concentrations were 32.4 μg/L and 34.1 μg/L respectively.

Differences in iodine excretion by region were also noted in die second screening cycle (Table 2). The highest iodine excretion was found in Kyiv city, where the median level was 68.0 μg/L, significantly higher than during the first cycle, as reflected in the non-overlapping confidence intervals. For the other regions (except Ivankiv raion), median urinary iodine excretion also increased from the first to the second

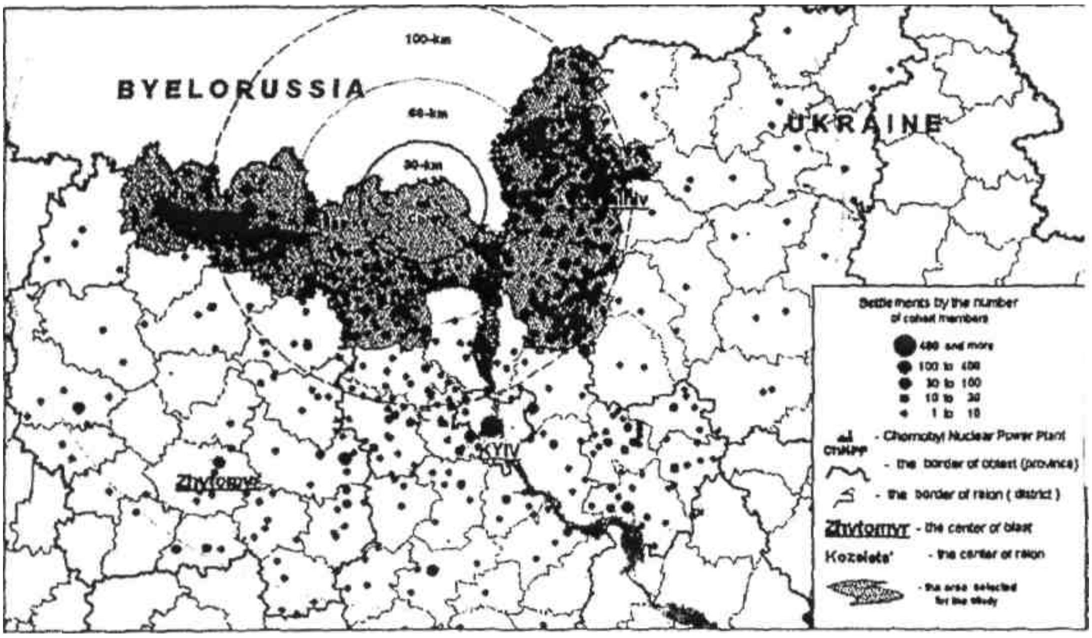

FIG. 1. Residency of cohort members at the time of the first cycle, 1998-2000.

screening cycle, although to absolute levels less than that of Kyiv city and Kyiv oblast.

A comparison of the overall median levels in Cycle 1 (41.7 μg/L, 95% CI 40.4-42.5) with those in Cycle 2 (475 μg/L. 95% CI 46.5-48.9) indicate an increase in levels in the second time period, an increase that remained significant even after accounting for within-person variability ($p = 0.01$, data not shown). Overall the relative increase in median urine concentrations was approximately 14%. Figure 2 illustrates this shift to higher values during the time of the second screening. The percent of cohort members with values of 100 μg/L or more indicating iodine sufficiency remains small, however (18% vs. 13% in the first cycle).

Tables 3 and 4 present data on urinary iodine for subgroups in Kyiv, Zhytomyr, and Chemihiv oblasts classified as urban or rural. The data for Cycle 1 (Table 3) show a significant urban/rural difference, with median concentrations of 48.9 μg/L (95% CI 47.0-49.9) in urban areas and 38.5 μg/L

TABLE 1. MEAN AND MEDIAN VALUES OF URINARY IODINE ACCORDING TO PLACE OF RESIDENCY: 1[st] CYCLE, 1998–2000

Study oblast	*Raion*	n	*Mean[a] μg/L*	*95% CI[b]*	*Median[a] μg/L*	*95% CI*
Zhytomyr	Narodichi	771	47.0	42.9–51.0	34.1	32.1–36.6
	Ovruch	2,100	50.0	47.3–52.6	32.4	31.2–33.8
	Other	418	53.6	48.1–59.0	38.9	35.5–42.1
Kyiv	Ivankiv	670	62.6	58.1–67.0	43.8	40.8–47.0
	Kyiv city	802	65.3	61.3–69.3	47.5	44.7–50.4
	Other	1,030	72.5	68.9–76.1	54.0	51.4–57.4
Chernihiv	Kozelets'	1,602	59.9	57.0–62.8	43.8	42.1–46.1
	Ripky	1,380	56.6	53.4–59.7	41.7	39.6–43.8
	Chernihiv	1,708	53.7	50.8–56.6	38.1	36.2–39.6
	Chernihiv city	1,384	68.5	65.4–71.6	51.9	49.4–54.6
Total		11,926[c]	58.6	57.1–60.0	41.7	40.4–42.5

[a]Model-adjusted for gender and age representing values for a 20-year-old female.
[b]95% confidence interval.
[c]Numbers do not add up to the column total because those places of residency where few cohort members resided ($n = 61$) were excluded to permit meaningful analysis.

TABLE 2. MEAN AND MEDIAN VALUES OF URINARY IODINE ACCORDING TO PLACE OF RESIDENCY: 2[nd] CYCLE, 2001–2003

Study oblast	Raion	n	Mean[a] µg/L	95% CI[b]	Median[a] µg/L	95% CI
Zhytomyr	Narodichi	706	57.7	52.3–63.1	38.9	36.6–41.7
	Ovruch	1,963	57.4	53.9–60.9	40.4	38.5–42.1
	Other	464	77.5	71.0–84.1	55.7	51.4–60.3
Kyiv	Ivankiv	663	63.0	57.4–68.7	40.8	37.7–43.8
	Kyiv city	852	100.6	95.7–105.6	68.0	64.1–72.2
	Other	1,080	89.8	85.2–94.3	60.9	57.4–64.7
Chernihiv	Kozelets'	1,650	70.9	67.2–74.5	51.4	48.9–53.5
	Ripky	1,352	60.4	56.4–64.5	42.5	40.4–44.7
	Chernihiv	1,646	60.9	57.1–64.6	40.8	39.2–42.9
	Chernihiv city	1,476	72.0	68.2–75.8	52.4	49.9–54.6
Total		11,939[c]	69.1	67.0–71.1	47.5	46.5–48.9

[a]Model-adjusted for gender and age representing values for a 20-year-old female.
[b]95% confidence interval.
[c]Numbers do not add up to the column total because those places of residency where few cohort members resided ($n = 87$) were excluded to permit meaningful analysis.

(95% CI 37.7-39.6) in rural areas, as is evident from the non-overlapping confidence Intervab. The higher median levels in urban compared to rural areas in Cycle 1 are most marked in Chemihiv oblast (51.4 µg/L vs. 40.4 µg/L). In Cycle 2, the difference is most striking in Kyiv oblast (66.0 µg/L in urban areas vs. 48.4 µg/L in rural areas), due in large measure to the significant increase in median urinary iodine concentrations in Kyiv city (47.5 µg/L vs. 68.0 µg/L). Although levels in Cycle 2 remain higher in urban areas relative to rural areas, the absolute levels in rural areas have increased significantly from Cycle 1 to Cycle Z

An analysis of the dietary questionnaire data from the first screening cycle shows that in the period 1998-2000 the population either did not take or only occasionally took iodi-

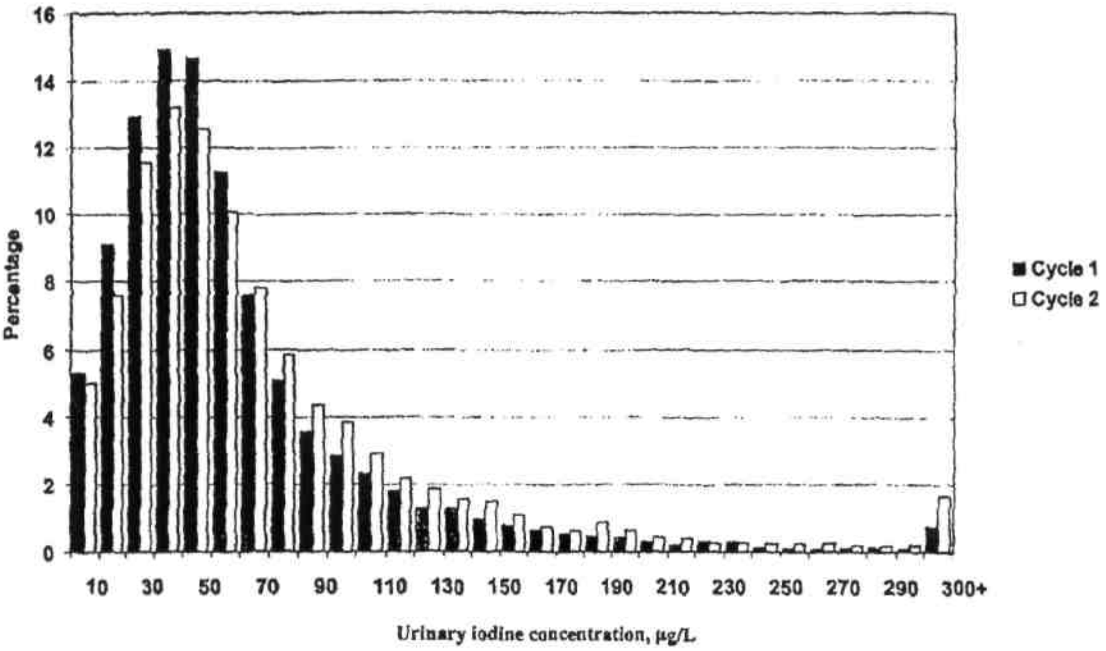

FIG. 2. Distribution of urinary iodine concentration during the 1[st] and 2[nd] screening cycles: Ukrainian-American study of thyroid cancer and other thyroid diseases following the Chornobyl accident.

TABLE 3. MEAN AND MEDIAN VALUES OF URINARY IODINE ACCORDING TO URBAN OR RURAL TYPE OF RESIDENCY: 1st CYCLE, 1998–2000

Study oblast	Raion	n	Mean[a] μg/L	95% CI[b]	Median[a] μg/L	95% CI
Zhytomyr	Rural	2,805	49.1	46.7–51.4	32.8	31.8–34.1
	Urban	484	53.6	48.6–58.7	38.9	35.9–42.1
Kyiv	Rural	1,172	67.7	64.3–71.2	48.4	46.1–51.4
	Urban	1,330	67.4	64.2–70.6	49.4	47.0–51.9
Chernihiv	Rural	4,410	55.9	53.9–57.9	40.4	39.2–41.7
	Urban	1,664	68.6	65.7–71.4	51.4	49.4–54.0
Total	Rural	8,387	55.1	53.5–56.8	38.5	37.7–39.6
	Urban	3,478	65.9	63.8–68.0	48.9	47.0–49.9

[a]Model-adjusted for gender and age representing values for a 20-year-old female.
[b]95% confidence interval.

nated preparations (iodinated salt, multivitamins containing iodine, or medications containing iodine: antistrumin, potassium iodide, thyroxine). For all localities, the frequency of taking these preparations did not exceed 5.4%; among the individuals taking these preparations, iodinated salt made up only 0.5% and iodine additives 0.2%. Use of these preparations had no noticeable effect on iodine excretion in urban and rural areas, presumably because the level of consumption of these preparations in the period 1998-2000 was so low.

Dietary data from the second screening cycle showed a significant increase in consumption of iodine-containing products. During the second cycle of screening, 1,743 (153%) cohort members reported using iodinated salt, as compared to 05% in the first cycle ($p < 0.01$, Fisher's exact test). A significant increase in consumption of other preparations and products containing iodine was also noted, although, in many cases, taking of iodinated preparations was sporadic. An analysis of intake data by place of residence for residents of urban and rural areas indicates that consumption of products and preparations containing iodine was somewhat higher in urban areas (data not shown).

Taking of iodine-containing medications, a supplement containing iodine, or iodinated salt appears to have had a noticeable effect on iodine excretion. Nevertheless, in spite of improvement in both consumption of iodine-containing preparations and levels of urinary iodine excretion, iodine sufficiency had not been achieved by the end of the second screening cycle in 2003.

Discussion

The data on levels of urinary iodine excretion collected by the Ukrainian-American Project have special significance. Beginning in 2001, the Ministry of Public Health and the Cabinet of Ministers of Ukraine issued decrees to establish national and regional programs for the elimination of iodine deficiency. Some of the data collected in this study are for raions that have not previously been surveyed, so they provide additional information on the sufficiency of iodine intake in Ukraine and the early impact of the public health programs in these areas.

Our measure of urinary iodine concentration is based on a casual sample. Although for logistical reasons we used a spot sample instead of a 24-hour collection, because the cohort is large, the means and medians for various subgroups are likely to correlate highly with the values we would have obtained from a 24-hour sample (11). The study has several strengths. Urinary iodine excretion data were available for 90% or more of the cohort, and the standardization for age

TABLE 4. MEAN AND MEDIAN VALUES OF URINARY IODINE ACCORDING TO URBAN OR RURAL TYPE OF RESIDENCY: 2nd CYCLE, 2001–2003

Study oblast	Raion	n	Mean[a] μg/L	95% CI[b]	Median[a] μg/L	95% CI
Zhytomyr	Rural	2,608	58.8	55.7–61.9	40.8	39.2–42.5
	Urban	525	69.4	63.2–75.6	48.9	45.2–53.0
Kyiv	Rural	1,203	72.2	67.8–76.6	48.4	46.1–51.4
	Urban	1,392	99.1	95.0–103.9	66.0	62.8–69.4
Chernihiv	Rural	4,359	64.1	61.5–66.7	44.7	43.4–46.1
	Urban	1,765	71.6	68.1–75.2	51.9	49.9–54.6
Total	Rural	3,682	62.9	60.7–65.2	43.8	42.5–45.2
	Urban	8,170	81.1	78.3–83.8	54.6	54.0–58.0

[a]Model-adjusted for gender and age representing values for a 20-year-old female.
[b]95% confidence interval.

and gender allowed for direct comparison of subgroups and for assessment of time and place variables independently of these demographic factors.

The results of this study show significant differences in urinary Iodine levels by place of residence and over time, adjusting for gender and age. Average and median excretion levels have increased significantly In the second screening cycle as compared to the first. This finding is consistent with dietary data from the first and second screening cycles which show an increase in the intake of iodine containing foods, salt, and supplements. Although urinary iodine levels have risen in both urban and rural areas, levels remain higher in urban areas.

In Cycle 1, the lowest levels of urinary iodine were in Zhytomyr oblast, in all of the raions examined and in the urban as well as rural portions of the area. Although the reasons have not been established, these levels may reflect the soil and water conditions of this region compared to Kyiv and Chemihlv oblasts. However, the situation in Zhytomyr improved in the time period corresponding to Cycle 2, particularly in urban areas, where access to public health messages and to iodine-containing salt and iodine-rich food is likely to be greater.

The significance of the findings reported here to Ukraine as a whole is that the programs to eliminate iodine deficiency seem to be having an impact. Although it is still too early for these programs to have succeeded in eliminating iodine deficiency, median levels have increased in both urban and rural areas and there has been a small increase in the percent of urinary iodine levels within the "sufficient" range. Nevertheless, the need for a strong program of iodination continues.

The findings reported here also indicate that the Ukrainian-American Cohort Study Is taking place in an environment where the levels of urinary iodine excretion, a marker for intake, now appear to be changing over time. In contrast, past investigations by other authors (14), along with previous studies by Tronko et al. (15) carried out with WHO support, were indicative of a stable situation with respect to iodine deficiency in the northern regions of Ukraine over a long period of time before the enactment of government programs in 2001. A retrospective analysis of the Iodine content in the soil and in subsoil waters (16) and indices of the prevalence of diffuse euthyroid goiter (14,15,17) suggest the presence of iodine deficiency in this region decades before the Chomobyi accident, at the time of the accident, and before the present investigations began. Judging from the results of this etudy, the situation seems to be changing. These findings will have to be accounted for when rates of cancer and other thyroid diseases are calculated over time, particularly since the impact of iodine intake on the occurrence of cancers is uncertain (18).

The findings from the present study show significant variation in urinary iodine concentrations by time and place and type of residency, and they suggest that intake of iodine-rich products may account in part for the observed increase in iodine levels from the first to the second time period.

Conclusions

Within the study area, levels of urinary iodine excretion vary by place of residence. Rural areas are characterized by lower levels of urinary iodine excretion than urban areas, but levels are increasing in both urban and rural areas. The study areas continue to be areas of moderate to mild iodine deficiency. As a result, cohort members have experienced and continue to experience insufficient iodine intake, which may contribute to the development of thyroid pathology.

Preventative measures to eliminate iodine deficiency prior to 2001 had a negligible impact on the study population: only 5.4% of the population reported consuming iodinated preparations on an ongoing basis in the first round of screening. Over the years 2001-2003, an improvement in iodine nutrition of the population was noted; a statistically significant increase in urinary iodine excretion was observed and the screening questions on consumption of products containing stable iodine indicate a statistically significant increase in intake. Continued attention to iodination is needed, however. Because iodine intake is a potential modifying factor In relation to thyroid cancer, information on iodine intake and sufficiency of intake has to be considered when evaluating rates of thyroid cancer and other thyroid diseases over time.

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