

## Thyroid Abnormality Trend Over Time in Northeastern Regions of Kazakstan, adjacent to the Semipalatinsk Nuclear Test Site: A Case Review of Pathological Findings for 7271 Patients

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### **Nuclear weapon testing/Semipalatinsk/Thyroid abnormalities/Pathological specimens/Radiation-induced neoplasms**

From 1949 through 1989 nuclear weapons testing carried out by the former Soviet Union at the Semipalatinsk Nuclear Test Site (SNTS) resulted in local fallout affecting the residents of Semipalatinsk, Ust-Kamenogorsk and Pavlodar regions of Kazakstan. To investigate the possible relationship between radiation exposure and thyroid gland abnormalities, we conducted a case review of pathological findings of 7271 urban and rural patients who underwent surgery from 1966–96. Of the 7271 patients, 761 (10.5%) were men, and 6510 (89.5%) were women. The age of the patients varied from 15 to 90 years. Overall, a diagnosis of adenomatous goiter (most frequently multinodular) was found in 1683 patients (63.4%) of Semipalatinsk region, in 2032 patients (68.6%) of Ust-Kamenogorsk region and in 1142 patients (69.0%) of Pavlodar region. In the period 1982–96, as compared before, there was a noticeable increase in the number of cases of Hashimoto's thyroiditis and thyroid cancer. Among histological forms of thyroid cancer, papillary (48.1%) and follicular (33.1%) predominated in the Semipalatinsk region. In later periods (1987–96), an increased frequency of abnormal cases occurred among patients less than 40 years of age, with the highest proportion among patients below 20 in Semipalatinsk and Ust-Kamenogorsk regions of Kazakstan. Given the positive findings of a significant cancer-period interaction, and a significant trend for the proportion of cancer to increase over time, we recommend

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more detailed and etiologic studies of thyroid disease among populations exposed to radiation fallout from the SNTS in comparison to non-exposed population.

## INTRODUCTION

For years, what happened at the Semipalatinsk Nuclear Test Site area and its effects on human health and the environment would be treated as classified information. From 1949 through 1962, 88 atmospheric and 30 surface atomic bomb tests were carried out by the former Soviet Union at the Semipalatinsk Nuclear Test Site (SNTS) in Kazakstan resulting in local fallout affecting the residents of Semipalatinsk, Ust-Kamenogorsk and Pavlodar Regions of Kazakstan<sup>1</sup>. The results of some dose reconstruction indicate a dose range of 2 mSv to 5 Sv, with most local residents being exposed to effective doses below 0.1 Sv<sup>2</sup>. However, there are no comprehensive data, describing dynamics of radioactive situation on territories adjacent to the SNTS from all atmospheric and surface nuclear explosions. It complicates reconstruction of effective and collective doses. At least four of these tests, on August 29, 1949 (22 kilotons), September 24, 1951 (38 kt), August 12, 1953 (400 kt), and August 24, 1956 (26.5 kt) resulted in substantial exposures to inhabitants of this region and are thought to have been responsible for about 95% of the collective radiation dose from fallout to residents of areas adjoining the SNTS. Although above-ground testing was terminated in 1962, the local population continued to be exposed to vented underground detonations, which occurred until 1989. During the period from 1962 to 1989, 340 underground nuclear explosions of nuclear weapons were conducted<sup>1</sup>. The thyroid gland is very sensitive to the carcinogenic effects of radiation. It is known, that the prevalence of thyroid nodules can be associated with radiation dose. Among exposed population the subsequent risk of thyroid cancer is highly dependent upon age at exposure. Several authors have suggested an increase in thyroid neoplasm among individuals who received external radiation to the thyroid gland<sup>3-6</sup>.

Given the association between radiation exposure and thyroid abnormalities, the present study was undertaken to describe characteristics of thyroid abnormalities among hospitalized patients and attempt to investigate the possible relationship between nuclear weapons testing at the SNTS and thyroid abnormalities in 3 regions adjacent to SNTS. Ust-Kamenogorsk and Pavlodar regions of Kazakstan are known as heavy industrialized and polluted regions, even during the former Soviet Union many factories of the heavy industry located in these regions. Semipalatinsk region is more agricultural and closest to SNTS. This study provides a description of the frequency of benign and malignant thyroid abnormalities among 7271 surgical cases in 3 regions of Kazakstan from 1966 to 1996. In addition, it can provide useful baseline information on thyroid diseases for reference in future investigations, because this paper reports the results of the first comprehensive investigation to study all reliable and valid information about thyroid abnormalities among hospitalized patients, which is available in 3 regions of Kazakstan adjacent to SNTS.

## MATERIALS AND METHODS

During the years 1966–96, 7271 patients with clinically palpable nodular or multinodular thyroid disease were referred to Regional hospitals of Semipalatinsk city, Ust-Kamenogorsk city and Pavlodar city with a recommendation for surgery, and underwent thyroid surgery there. Fine needle biopsy (FNB), ultrasound examinations were not routinely used in the evaluation of such patients in Kazakhstan during that time and a practice of the former Soviet Union's surgical hospitals differed from Western countries. All information in the present study is based on final surgical pathologic diagnosis abstracted from records of the Regional Pathological Laboratory of 3 regions of Kazakhstan and medical records of Regional Hospitals. Usually, pathologists submitted the total surgical specimen to do serial sections. Final surgical pathologic findings adopted as the most reliable data for diagnosis of thyroid abnormalities.

Of the 7271 patients, 761 (10.5%) were men, and 6510 (89.5%) were women. The age of the patients varied from 15 to 90 years, and they came from both urban and rural areas. Patients were examined in various health care facilities in Semipalatinsk city, Ust-Kamenogorsk city and Pavlodar city. Preoperative management of the patients was carried out in accordance with generally accepted procedures. Patients with thyrotoxic manifestations were managed with a conservative course of antithyroid drug therapy in an endocrinology clinic until euthyroidism was achieved prior to resection. Patients with a clinically solitary nodule underwent enucleation of the nodule with resection of surrounding tissue or subtotal lobectomy as indicated. In cases of multinodular goiter, subtotal subfascial resection of the affected thyroid tissue was performed. It should be noted that it was clinically very difficult to make a preoperative diagnosis of thyroid cancer, because of the lack of FNB, ultrasound examination and the paucity of other diagnostic resources available to regional hospitals. That is why in cases of intraoperative suspected thyroid cancer, the affected part of the gland was extirpated, including surrounded tissue and affected lymph nodes dissection was done or bilateral near-total thyroidectomy performed as indicated in some cases. There was no operative mortality. In all cases, the surgically resected material was sent to the Regional Pathological Laboratory in each region for histological study, where diagnoses were given according to the World Health Organization criteria. The methods for the processing and sectioning of the surgical specimens were the same in all Regional Pathologic Laboratories. If thyroid cancer was confirmed, the patient was sent to the Regional Oncological Dispansery for the further management.

Histologic diagnoses for the present study were provided by local pathologists at the Regional Pathological Laboratory of the Semipalatinsk, Ust-Kamenogorsk and Pavlodar regions. In addition, 50 randomly selected cases were reviewed by 3 pathologists from different institutions (Baylor College of Medicine, Houston, Texas; Hiroshima University, Japan and Semipalatinsk State Medical Academy, Kazakhstan) to assess the previously rendered diagnoses and quality of the histological specimens. A 100% concordance rate was observed by the reviewers.

In order to address period effects and secular trends we divided the calendar years of

study into 6 strata: Period I; 4–9 years afterwards (1966–1971), Period II; 10–14 years afterwards (1972–1976), Period III; 15–19 years afterwards (1977–1981), Period IV; 20–24 years afterward (1982–1986), Period V; 25–29 years afterwards (1987–1991), and Period VI; 30–34 years afterwards (1992–1996).

Linear categorical analysis was performed by regressing the ratio of the number of cases out of the total cases for each period on seven indicator variables for each surgical outcome, six time periods mentioned above, and six interaction terms for cancer and the period. Simultaneous tests of significance for several regression coefficients were carried out<sup>7)</sup>.

## RESULTS

Table 1 shows a frequency distribution of 7271 thyroid abnormalities among surgical patients in 3 regions of Kazakhstan adjacent to SNTS. The total number of thyroid abnormalities was 2962 in Ust-Kamenogorsk region. Of the 2962 patients, 373 (12.6%) were men and 2589 (87.4%) were women, the male/female ratio was 1 : 7. Of the 2653 patients from Semipalatinsk region, 200 (7.5%) were men and 2453 (92.5%) were women, the male/female ratio was 1 : 12. Of the 1656 patients from Pavlodar region, 188 (11.3%) were men and 1468 (88.7%) were women, the male/female ratio was 1 : 8. The total number of thyroid cancer and Hashimoto's thyroiditis predominated in the Semipalatinsk region. The total number of benign adenoma predominated in the Pavlodar region. Overall, a diagnosis of adenomatous goiter (most frequently multinodular) was found in 1683 patients (63.4%) of Semipalatinsk region, in 2032 patients (68.6%) of Ust-Kamenogorsk region and in 1142 patients (69.0%) of Pavlodar region. In all regions the thyroid abnormalities rate was higher in females than in males in most age groups. The male/female ratio was 1 : 28 among patients with Hashimoto's thyroiditis in Semipalatinsk region, 1 : 29 in Ust-Kamenogorsk region and 1 : 16 in Pavlodar region. A break-down of diagnoses over each of the study periods among patients in the Semipalatinsk region and also several interesting trends are given in Table 2. The total number of surgical cases increased over the years, especially after 1982. This increase was

**Table 1.** Frequency distribution of 7271 thyroid abnormalities among surgical patients in 3 regions of Kazakhstan adjacent to SNTS

Abnormality	Semipalatinsk		Ust-Kamenogorsk		Pavlodar		Total	
	number	%	number	%	number	%	number	%
Goiter	1683	63.4	2032	68.6	1142	69.0	4857	66.8
Adenoma	361	13.6	432	14.6	356	21.5	1149	15.8
Cancer	239	9.0	164	5.5	93	5.6	496	6.8
Hashimoto's thyroiditis	318	12.0	304	10.3	53	3.2	675	9.3
Riedel's thyroiditis	16	0.6	23	0.8	10	0.6	49	0.7
de Quervain's thyroiditis	12	0.5	1	0.03	1	0.1	14	0.2
Others	24	0.9	6	0.2	1	0.1	31	0.4
Total	2653	100	2962	100	1656	100	7271	100

**Table 2.** Frequency distribution of 2653 thyroid abnormalities among surgical patients in the Semipalatinsk region of Kazakhstan

Calendar period	Goiter (all forms)	Adenoma	Number of cases diagnosed pathologically (%)					Other	Total
			Cancer	Hashimoto's thyroiditis	Riedel's thyroiditis	de Quervain's thyroiditis			
I (1966–1971)	324 (83.9)	12 ( 3.1)	5 ( 1.3)	37 ( 9.6)	3 (0.8)	3 (0.8)	2 (0.5)	386 (100)	
II (1972–1976)	212 (59.9)	95 (26.8)	16 ( 4.5)	25 ( 7.1)	1 (0.3)	0 (0.0)	5 (1.4)	354 (100)	
III (1977–1981)	229 (60.4)	85 (22.4)	17 ( 4.5)	36 ( 9.5)	5 (1.3)	1 (0.3)	6 (1.6)	379 (100)	
IV (1982–1986)	276 (60.1)	59 (12.9)	48 (10.5)	69 (15.0)	1 (0.2)	1 (0.2)	5 (1.1)	459 (100)	
V (1987–1991)	353 (54.6)	68 (10.5)	105 (16.3)	111 (17.2)	4 (0.6)	2 (0.3)	3 (0.5)	646 (100)	
VI (1992–1996)	289 (67.4)	42 ( 9.8)	48 (11.2)	40 ( 9.3)	2 (0.5)	5 (1.2)	3 (0.7)	429 (100)	
Total	1683 (63.4)	361 (13.6)	239 ( 9.0)	318 (12.0)	16 (0.6)	12 (0.5)	24 (0.9)	2653 (100)	

largely accounted by a rise in Hashimoto’s thyroiditis and thyroid cancer, particularly during periods IV and V. Although the number of cases of adenomatous goiter increased from periods II to V, the percentage remained relatively constant. Diagnosis of benign adenoma steadily decreased through the majority of the study. Lastly, the rates of Riedel’s and de Quervain’s thyroiditis, as well as other conditions (tuberculosis, cyst, hematoma) went relatively unchanged during the study periods.

A major goal in this investigation was to determine whether there has been an increase in the proportion of thyroid cancers identified throughout the time periods. In the “Cancer” column of Table 2, one can notice the proportion of cancer out of all other outcomes increases over time. Although inferences can be made by visualizing non-zero effects and increasing trends of proportions, we nevertheless performed hypothesis tests to discredit the null hypothesis of no period effect, no cancer-period interaction, and no trend of the cancer-period interaction. Results of the  $\chi^2$  tests were 4575.67 (6 d.f.) for the period effect, 164.99 (6 d.f.) for the cancer-period interaction and 64.18 (1 d.f.) for the test of trend for the cancer-period interaction. These results indicate that there is a significant period effect, a significant cancer-period interaction, and a significant trend for the proportion of cancer to increase over time.

We documented that the male/female ratio was 1 : 6 and 1 : 8 during period IV and V respectively, among patients with thyroid cancer compared with ratio 1 : 4 during period I and II. This ratio was 1 : 35, 1 : 33, 1 : 27 during period III, IV and V respectively, among patients with Hashimoto’s thyroiditis versus 1:17 during period I. In all 3 regions the total number of thyroid cancer increased gradually over the years as shown in Table 3. This increase was more marked in Semipalatinsk region, especially during period IV and V. The total number of undifferentiated thyroid cancer increased during period V as well. Overall, papillary and follicular cancers predominated as shown in Table 4. Pathologists noted a frequent co-occurrence of various forms of thyroid cancer and Hashimoto’s thyroiditis, as well as occasional cancers with multinucleated giant cells or Hurthle-cell transformation. It should be noted that most cancers were localized. Metastatic tumor rate was very low in all regions.

Additional analysis revealed that in study periods IV and V, younger patients (under 40) were particularly affected, and an increased occurrence of cancer was noted in patients 15–20

**Table 3.** Frequency distribution of 496 thyroid cancer in 3 regions of Kazakhstan

Calendar Period	Semipalatinsk		Ust-Kamenogorsk		Pavlodar		Total	
	number	%	number	%	number	%	number	%
I (1966–71)	5	1.3	2	0.6	1	0.3	8	1.6
II (1972–76)	16	4.5	2	0.7	1	0.4	19	3.8
III (1977–81)	17	4.5	28	7.4	7	3.5	52	10.5
IV (1982–1986)	48	10.5	50	5.7	13	5.4	111	22.4
V (1987–91)	105	16.3	36	5.7	30	10.8	171	34.4
VI (1992–96)	48	11.2	46	10.1	41	10.7	135	27.2
Total	239	48.2	164	33.1	93	18.7	496	100

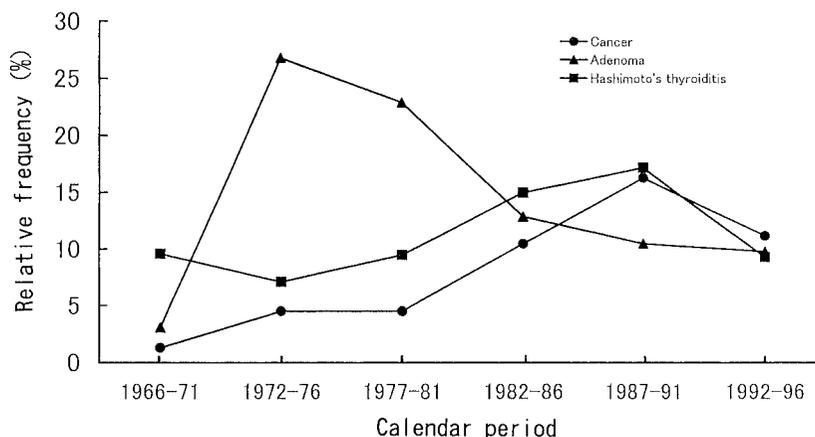
**Table 4.** Frequency distribution of 496 thyroid cancer subtypes in 3 regions

Histological forms	Semipalatinsk		Ust-Kamenogorsk		Pavlodar		Total	
	number	%	number	%	number	%	number	%
Papillary	115	48.1	85	51.8	48	51.6	248	50
Follicular	79	33.1	50	30.5	21	22.6	150	30.2
Medullary	12	5.0	1	0.6	0	0.0	13	2.6
Squamous Cell	4	1.7	1	0.6	1	1.1	6	1.2
Undifferentiated	5	2.1	1	0.6	6	6.4	12	2.4
Unclassified	24	10.0	26	15.9	17	18.3	67	13.5
Total	239	100	164	100	93	100	496	100

**Table 5.** Age distribution among patients with thyroid cancer in 3 regions

Regions	Under 19		20–29		30–39		40–49		50–59		60 and >		Total	
	number	%	number	%	number	%	number	%	number	%	number	%	number	%
Semipalatinsk	16	6.7	34	14.2	66	27.6	60	25.1	40	16.7	23	9.6	239	48.2
Ust-Kamenogorsk	5	3.0	25	15.2	46	28.0	35	21.3	29	17.7	24	14.6	164	33.1
Pavlodar	0	0.0	10	10.8	18	19.4	24	25.8	20	21.5	21	22.6	93	18.7
Total	21	4.2	69	14.0	130	26.2	119	24.0	89	17.9	68	13.7	496	100

years old, especially in Semipalatinsk and Ust-Kamenogorsk regions. Table 5 shows that the absolute number and percentage of the thyroid cancer was higher in patients aged 30–39 years, especially in Semipalatinsk and Ust-Kamenogorsk regions. It is interesting to note some features of the relationship between time trend of the thyroid cancer, adenoma and Hashimoto's thyroiditis in the Semipalatinsk region (Fig. 1). We can see that an increase in the incidence of thyroid cancer and Hashimoto's thyroiditis accompanies by substantial decreasing in the incidence of adenoma in Semipalatinsk region. This finding may indicate a possible role of adenoma also in the development of thyroid cancer as well as other conditions. At the same time in Ust-Kamenogorsk and Pavlodar regions we revealed that an increase in the total number of thyroid cancer and Hashimoto's thyroiditis accompanied by



**Fig. 1.** Time trend of the thyroid cancer, Hashimoto’s thyroiditis and adenoma in the Semipalatinsk region of Kazakhstan (1966–1996).

increasing in the total number of adenoma as well. The percentage of adenomatous goiter gradually decreased in Ust-Kamenogorsk and Pavlodar regions over the years. In Semipalatinsk region the percentage of adenomatous goiter decreased during period II and after that remained relatively constant. In a number of instances, multiple abnormalities were found in a single specimen, such as a cancer in the presence of Hashimoto’s thyroiditis. This finding may indicate a role of Hashimoto’s thyroiditis in the development of thyroid cancer. It has been suggested that autoimmune conditions may reduce the thyroid gland’s resistance to neoplastic processes in the presence of iodine-131<sup>8)</sup>. Additionally, the coexistence of benign and malignant lesions has been suggested by previous histopathological studies of patients with a history of radiation exposure<sup>9,10)</sup>.

### DISCUSSION

By virtue of the various reasons, including secrecy around SNTS the comprehensive study of radiation-induced thyroid abnormalities in the Semipalatinsk Nuclear Test Site area never has been done before, the present study is the first of its kind to investigate thyroid abnormalities in 3 major regions adjacent to SNTS. Furthermore, it is unique in that the medical standard of care provided us with a case series of 7271 surgical specimens with pathologic diagnoses.

Numerous publications have clearly demonstrated that the thyroid gland is one of the most radiosensitive organs in the human body<sup>3,6,11,12)</sup>. They confirmed the carcinogenic effect of ionizing radiation with respect to thyroid cancer and other malignant tumors as well, and have showed an increase in the incidence of radiation-associated thyroid disease in areas surrounding the nuclear test site.

Our investigation demonstrates as well an increase in the total number of surgical cases

in the 3 regions of Kazakstan 20–29 years after the onset of population exposures. This increase is largely due to increases in Hashimoto's thyroiditis and thyroid cancer, which increased progressively in periods II–V particularly in Semipalatinsk region. Statistical data collected by the Pathological Laboratory in Semipalatinsk, Ust-Kamenogorsk and Pavlodar indicate that the thyroid cancer rate did not exceed 3–5% from 1960–1970. Yet our study noted substantially higher rates of cancer after 1982, with thyroid cancer accounting for 16.3% of diagnoses during period V in the Semipalatinsk region. In the Ust-Kamenogorsk region the thyroid cancer rate was 5.7% during period V and 10.8% in the Pavlodar region. Some studies have suggested that the excess risk peaked 15–19 years after radiation exposure, then declined, although an excess at 40 years was still apparent<sup>6,11,12</sup>. It is of interest to do additional observations until lifetime risks can be characterized accurately. It is also interesting to note the relatively high percentage of follicular cancers after 1982, whereas most other studies have found an increase primarily in papillary forms of cancer following radiation exposure<sup>13,14</sup>. In our study we noted that the total number of thyroid cancer predominated among women. It is known that the increased risk in women has been linked to reproductive factors<sup>15,16</sup>. Unfortunately, we could not get any information on reproductive factors in this study. Ron et al<sup>6</sup>) suggested that the excess relative risk was higher among women, reflecting their higher rate of naturally occurring thyroid cancer.

In our study we revealed that an increase in the total number of thyroid cancer and Hashimoto's thyroiditis accompanied by noticeable decreasing in the total number of benign adenoma over the years in Semipalatinsk region. Silverberg and Vidone<sup>17</sup>) suggested that some thyroid carcinomas appear de novo, others begin as adenomas. They concluded that only something close to serial sections through an entire adenoma will enable the pathologist to state, with any degree of confidence, that he is not dealing with an early carcinoma. More detailed studies can provide fundamental information about the pathogenesis of thyroid neoplasia. At the same time we noted that in Ust-Kamenogorsk and Pavlodar regions an increase in the total number of thyroid cancer and Hashimoto's thyroiditis accompanied by gradually increasing in the total number of benign adenoma over the years. It should be noted that in Semipalatinsk and Ust-Kamenogorsk regions compared with Pavlodar region the thyroid cancer has clustered among younger adults, especially in study periods IV and V. Statistical data of the Pathological Laboratory of Semipalatinsk, Ust-Kamenogorsk and Pavlodar regions indicated that during 1960–1970 the average age was 50 years for all patients with thyroid cancer. It is important to know about age at first exposure. It has been reported that there is a trend for decreasing risk with increasing age at irradiation<sup>4,6</sup>). There are a number of difficulties associated with attempts to establish a causal relationship between radiation exposure and thyroid abnormalities, including inadequate dosimetric data, changes in medical screening over time, effect of sampling technique, information bias and many issues remain unresolved because of insufficient data in individual studies<sup>4,5,18–22</sup>). While the present study does not attempt to establish a casual relationship, it does suggest that the increase in observed cases of Hashimoto's thyroiditis and thyroid cancer may be related to the hundreds of nuclear weapons testing which took place at the SNTS from 1949–89.

Additional and etiologic studies are now in progress including analysis and estimation of

the underlying rates of benign and malignant thyroid diseases, in the heavily exposed regions and lightly exposed regions. They also include reconstruction of individual dosimetric data from recently declassified military records by using the various mathematical models and reevaluation of dosimetry systems. It is necessary to verify estimated radiation doses for high-exposure and low-exposure inhabitants, using cytogenetic assay of stable chromosome aberrations in peripheral lymphocytes. Further analysis may also permit us to assess whether the course of radiation-induced thyroid cancer is more aggressive and to determine the factors which influence the behavior of thyroid cancers. Finally, with increased awareness, implementation of the complex uniformed thyroid screening methodology using FNB and a high-resolution ultrasonography examination as well as examinations of blood specimen and thyroid antibody measurements should facilitate the early detection of benign and malignant thyroid diseases and ensure better monitoring and rehabilitation of exposed populations around Semipalatinsk Nuclear Test Site.

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