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Radiation and Thyroid Diseases : Experiences in Nagasaki and around Chernobyl

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The needs of a society are closely related to medical progress and its contribution. For instance, research on AIDS and cancer is carried out to meet the demand of contemporary society. Thyroid disease caused by iodine deficiency is one such challenge, and "radiation and thyroid" is another major research theme. Clinical investigation and basic research on radiation-induced thyroid diseases through molecular epidemiology have received much attention from scientists in Nagasaki because of our historical background of atomic bomb exposure and accumulated data of radiation-induced human diseases. We, therefore, introduce the experiences of thyroid examination in Nagasaki and Chernobyl and epidemiological analysis of the effect of radiation on thyroid diseases.

Background scientific knowledge

External radiation is known to cause of thyroid cancer, but radioactive iodine has been used for many years in the treatment of thyrotoxicosis without any increase in thyroid carcinoma. The majority of cases of thyroid carcinoma following exposure to X-ray are papillary in histological type, the latent period is about 5-10 years, sensitivity decreased with increasing age at exposure, and an increase in the risk of thyroid cancer persisted for decades.

The thyroid gland is one of the ideal organs for the investigation on radiation-induced disease for the following reasons :

1) The thyroid takes up radioactive iodine (internal radiation) and the thyroid is a relatively sensitive organ to external radiation, especially in children.

2) Patients with thyroid disease can survive for a long time with or without treatment and the survey can be conducted using the same protocol to examine all subjects in a cohort at the same time.

3) The prevalence of thyroid disease in the general population is higher than that of other radiation-induced diseases and this high prevalence in normal control is an advantage for epidemiological studies.

These principles are applicable to the analytical approaches of the late affect of internal as well as external radioactive exposures on thyroid disease although ^{131}I is considered to be less carcinogenic than acute exposure to X-rays.

To investigete the health effects of radiation on the thyroid, the following three are essential to obtain a significant result :

1) Determination of the exact thyroid radiation dose.

2) Correct diagnosis of thyroid diseases.

3) Analysis of the results by the most appropriate statistical method.

At every nuclear weapons test and nuclear accident, huge doses of radioactive iodine have been released which can affect the thyroid gland as an internal radiation.

The Chernobyl accident on April 26, 1986 at 1 : 23 pm is the only instance of the radiation exposure of a large population at relatively high levels followings a nuclear accident. Large amounts of radioactive materials were released and one of the main constituents was ^{131}I. In the symposium on "Radiation and the Thyroid" held at the meeting of the Japanese Society of Nuclear Medicine in Nagasaki City in October, 1987, worldwide ^{131}I fallout in animal thyroid gland, during the period from 1954 to 1987 was shown by Van Middlesworth L[1]. He also showed the ^{131}I levels in animal thyroids immediately after the nuclear reactor accident at Chernobyl. Even in Germany, United Kingdom, United States and Japan which are far from Chernobyl, the increase of ^{131}I levels in animal thyroid after the accident was observed[1]. Present estimates suggest that ^{131}I with an activity of 1.8×10^{18} Bq was released. The deposition of radioactive materials from tha Chernobyl accident was complex and was affected by wind and rainfall over the period of intense radioacitive releases, which lasted biologically more than 3-6 months.

In this manuscript, thyroid diseases in atomic bomb survivors in Nagasaki and in children after the Chernobyl accident will be introduced because of the different type of radiation exposure and the effects of the thyroid in children exposed to radiation will be discussed mainly as a result of the Chernobyl accident.

Experience in Nagasaki

The current status of thyroid diseases for the Nagasaki Adult Health Study cohort of the Radiation Effects Research Foundation was reported in JAMA[2]. The subjects were cohort members of the Nagasaki Adult Health Study and 2856 subjects who visited for biennial health examinations from 1984 to 1987 participated in the study. Thyroid radiations dose in each subject were determined using the Dosimetry System 1986 (DS86), and the thyroid diseases in each subject were screened using thyroid ultrasonography, measurements of serum levels of thyroxine (T_4), free T_4 (FT_4), triiodothyronine (T_3), thyroid-stimulating hormone (TSH), thyroglobulin and titers of autoantibodies. Subjects with any physical or laboratory abnormalities were referred to the Nagasaki University Clinic for the final diagnosis. Statistical analysis of the prevalence of thyroid disease was performed using linear logistic models with sex, age at the time of atomic bombing and DS86 thyroid radiation dose. A significant correlation was found between the thyroid radiation dose and the prevalence of thyroid disease in thyroid solid nodules and thyroid carcinoma in women and antibody-positive spontaneous hypothyroidism (Fig. 1). The prevalence of thyroid nodule increases monotonously with thyroid radiation dose and the prevalence is significantly higher as the age at the time of bombing is decreased (Fig. 2). However, the prevalence of antibody-positive spontaneous hypothyroidism (autoimmune hypothyroidism) displayed a convex dose-response relationship with a maximum level of 0.7 Sv. Significant increase in autoimmune disease among atomic-bomb survivors is demonstrated for the first time in this study, 45 years after the atomic bomb explosion. Based on the knowledges and experience of the follow-up studies of atomic bomb survivors in Nagasaki, we have applied our know-how to the health screening program around Chernobyl since May, 1991

International Chernobyl projects

While numerous reports have appeared on thyroid diseases in children after the Chernobyl accident, a unanimous conclusion could not be reached. Furthermore, conclusions had changed over time. The reports on the health consequences after the accident have been reviewed chronogically as follows. In 1991, the report published from the International Atomic Energy Agency (IAEA) concluded that, at the time of project study, these were significant non-radiation-related health disorders in the populations of both surveyed contaminated and surveyed control settlements, but no health disorders that could be attributed directly to radiation exposure[3]. A part of the results on thyroid investigation was published in JAMA by Mettler, et al[4], and the prevalence of thyroid nodules was not different between contaminated and control settlements. In 1992, however, it was reported in *Nature* that the number of children with thyroid cancer increased in Belarus[5] and this correspondence was supported[6], against which three comments were also published in the next number of *Nature*[7][8][9]. Many reports on the consequences of the Chernobyl accident became confused in 1992.

The effects on health of nuclear accidents are due to multiple factors including radiation as well as psychological and social effects, economic and political factors, desire for compensation and so on. Each of these factors has considerable influence on the health of people. In particular, there are several specific problems around Chernobyl.

1. The radiation-contaminated area around Chernobyl is

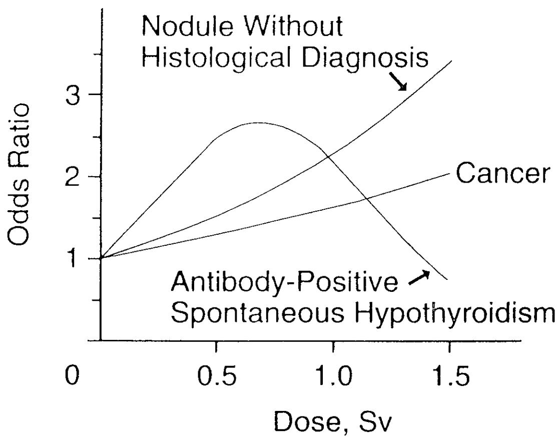

Fig. 1 Odds ratios of the prevalence of nodules without histological diagnosis (women only), cancer, and antibody-positive spontaneous hypothyroidism. From Ref. (2).

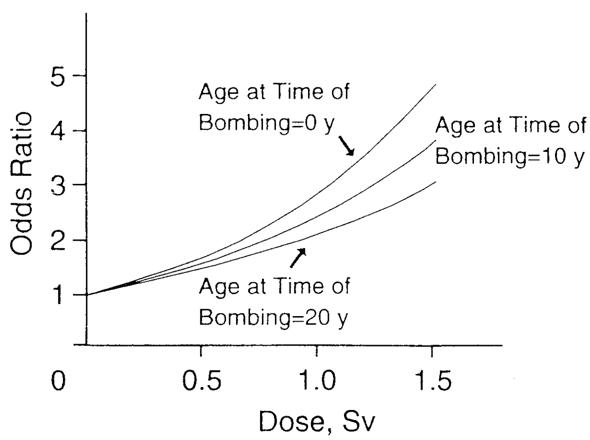

Fig. 2 Odds ratios of the prevalence of solid nodule famales exposed at 0, 10, and 20 years of age. From Ref. (2).

an endemic iodine-deficient zone.
2. The method of investigation is not always the same among the three republics : russia, Republic of Belarus and The Ukraine, after each republic became independent.

At times such as the Nagasaki symposium on Chernobyl update and future held on June, 1994[10]. The purpose was to discuss the scientific data from all over the world independently of psychological, social, economic and political bias, and to make conclusions that would further medical science. Many scientists from the former Soviet Union, World Health Organization (WHO), European Community (EC), USA, and Japan attended the symposium. In brief, the conclusions of Nagasaki symposium on Chernobyl update and future in 1994 were as follows :
1. Nine of 11 symposiasts believed the incidence of thyroid cancer definitely increased after the Chernobyl accident.
2. All symposiasts did not agree with the conclusion that thyroid cancer is definitely caused by radiation. However, all symposiasts agree that radiation is probably a cause of thyroid cancer and that the relation between thyroid cancer and radiation should be investigated.

As 1995 was the 50th year since the atomic bombs were dropped on Hiroshima and Nagasaki, we had another important symposium, "Nagasaki Symposium on Radiation and Human Health" to further extend our contribution to the world. The results of health consequences from the Chernobyl accident were renewed and re-evaluated by international specialists. The participants understood that there was storong evidence that the increased incidence of childhood thyroid cancer was due to radiation exposure as a result of the Chernobyl accident, based on the geographical and temporal distribution of the cases. Now the on-going Chernobyl projects will be introduced.

Fig. 3 Locations of the five centers of Chernobyl Sasakawa Project. From Ref. (18).

Experiences around Chernobyl

Several thyroid projects in Chernobyl are still under way. Among them, the Chernobyl Sasakawa project is the biggest[11]. Actual investigation started in 1991 and in these 5 years, more than 100,000 children were investigated. All members of the project on thyroid disease are from Nagasaki University School of Medicine. Learning by trial-and-error, a support system has been established taking into account the actual condition of each center. Examination skills of staff members have improved dramatically. In this project, centers for investigation were established in 5 regions : Klincy in Russian Federation, Mogilev and Gomel in Republic of Belarus and Kiev and Korosten in The Ukraine (Fig. 3). Methods of investigation include : 1) the exact history of each subject, 2) thyroid ultrasonic scanning, 3) measurements of serum levels of FT_4, TSH and titers of thyroid autoantibodies, 4) measurements of urinary iodine, 5) fine needle aspiration biopsy in subjects with goiter and/or nodule[12]. These method and protocols are essentially the same at all 5 diagnostic centers and the same as those used to evaluate Nagasaki atomic bomb survivors. Goiter was defined as a thyroid volume exceeding the upper limit of normal.

Measurement of the whole-body concentration and the contamination levels of ^{137}Cs in soil was performed on each child together with thyroid examination. To determine the ^{137}Cs concentration in children's bodies, direct spectrometry of radionuclide activity was performed. This method is based on the registration of gamma radiation from the body. The details of the methods of dosimetry were described previously[13][14].

The results of screening conducted in association with the Chernobyl Sasakawa project were reported every year[15][16][17][18] (Tables 1, 2). In brief, goiter is more prevalent in Kiev and thyroid autoantibodies in Korosten is more prevalent than those in Mogilev where is less contaminated and not iodine deficient. The reason of high prevalence of goiter in Kiev may be due to iodine deficiency. Children with thyroid cancer confirmed by histology were as follows : 2 in Mogilev, 25 in Gomel, 6 in Kiev, 5 in Korosten and 4 in Klincy (until 1995). In the Gomel region, the prevalence of thyroid cancer was especially high. All cases were histologically papillary carcinoma and the characteristics of thyroid cancer were highly invasive which in similar to childhood thyroid cancers in other parts of the world[19].

Since less than 20,000 children were screened in each center, the prevalence of thyroid cancer in not only the Gomel region but also in other regions was remarkably high (lowest 100 and highest 1000/million children) when compared to that of USA, Europe and Japan (0.2 to 5/ million per year)[20][21][22].

Based on this screening system, the incidence of childhood thyroid diseases around Chernobyl is shown to vary among the regions, as seen in Tables 1 and 2. In contrast to atomic-bomb survivors in Nagasaki, the thyroid radiation dose of these subjects is unknown. Therefore, it is impossible to caculate the thyroid dose-response relationship. The only radiation dose that could be obtained is the whole-body ^{137}Cs radioactivity, which, because of its long half-life, persisted so long after the Chernobyl accident in individual human bodies and in the soil. At the end of investigations of 86,000 children, no significant correlation between whole-body ^{137}Cs radioactivity and thyroid abnormalities were observed at any of the 5 centers[23] (Table 3).

Comments on radiation-induced Thyroid diseases around Chernobyl

Ten years after the Chernobyl accident, three big symposia were held in succession in November 1995, March 1996, and April 1996 by WHO, EC, and IAEA, respectively.The conclusions of the last symposium were as follows[24]:

There has been a substantial increase in the incidence of thyroid cancer, especially in young children. Thyroid cancer in individuals who were children at the time of the accident will be the form of cancer most likely to be manifest as a result of the accident. This is because of : (1) the high thyroid doses compared with doses to other parts of the body, (2) the vulnerability of children to thyroid cancer and (3) the low baseline incidence of thyroid cancer, especially in children.

Table 1 Results (I) of thyroid disorders (goiter, nodules, cancer).

	Number of Children	Goiter %	Nodule (S) Number	%	Cancer Number	%
BELARUS						
Mogilev	17,927	6−31	21	0.12	2	0.011
Gomel	14,054	4−56	254*	2.03*	19*	0.135*
UKRAINE						
Kiev	18,848	38−75*	31	0.17	6	0.032
Korosten	18,792	12−49	52	0.28	5	0.027
RUSSIA						
Klincy	17,467	31−53*	89*	0.52*	4	0.023

Table 2 Results (II) of thyroid disorders (thyroid dysfunction, positivity of anti-thyroid antibodies).

	Number of Children	Thyroid Dysfunction				Anti-thyroid-Antibody			
		Hyperthyroidism		Hyperthyroidism		Anti-thyroglobulin		Anti-microsome	
		Number	%	Number	%	Number	%	Number	%
BELARUS									
Mogilev	17,927	28	0.17	12	0.07	180	1.1	306	1.9
Gomel	14,054	24	0.18	40*	0.30*	134	1.0	347*	2.6*
UKRAINE									
Kiev	18,848	16	0.09	7	0.04	226	1.2	399	2.1
Korosten	18,792	14	0.07	24	0.13	535*	3.1*	591*	3.5*
RUSSIA									
Klincy	17,467	9	0.05	15	0.09	213	1.2	303	1.8

Table 3 Prevalence of thyroid diseases and whole-body ^{137}Cs radioactivity.

	BELARUS		UKRAINE		RUSSIA
	Mogilev	Gomel	Kiev	Korosten	Klincy
Goiter	N. S	N. S	N. S	N. S	N. S
Cancer		N. S	N. S		
Autoantibody					
Anti-thyroglobulin	N. S	N. S	N. S	N. S	N. S
Anti-microsome	N. S	N. S	N. S	N. S	N. S

The total number of childhood thyroid cancers found after the Chernobyl accident (1986-1994) is 880 in Belarus[25] (Fig. 4), The Ukraine[26] (Fig. 5), and Russia (Fig. 6). Childhood thyroid cancer has been increasing rapidly since 1990 around Chernobyl and no signs of a decrease are in sight. While a significant correlation between the thyroid radiation dose and the prevalence of thyroid disease was found in thyroid solid nodules and thyroid carcinoma in female among atomic bomb survivors in Nagasaki, so far there is no relationship between the occurrence of childhood thyroid diseases and the whole-body and soil ^{137}Cs levels around Chernobyl. As mentioned above, determination of the thyroid radiation dose is essential to reach to a signficant conclusion on the effect of radiation on subjects living in the contaminated areas.

Although many international experts agree that the increase of thyroid cancer is probably due to the radioactive fallout from the Chernobyl accident[27][28], it is still unknown what kind of radioactivity is the main cause of the increase in thyroid cancer. It is essential to show the dose-response from specific causal radioactive materials. The possible radioactive materials include various radioactive iodine isotopes which accumulate in the thyroid.

A map of ^{131}I contamination measured in 1986 was presented recently and it was reported that a significant dose-response was found between the prevalence of thyroid cancer and ^{131}I in the soil or the reconstructed thyroid ^{131}I dose[29]. However, it should be noted that there are no previous publications which showed that ^{131}I at any dose produced thyroid cancer in humans. The therapeutic dose of ^{131}I clearly induces hypothyroidism within several weeks after radiation. No reports, however, have been published which implicate ^{131}I as a cause of thyroid cancer in humans. On the contrary, several reports showed that no significant thyroid diseases were induced by the diagnostic dose of ^{131}I.

With regard to the Chernobyl accident, however, we have to take note of several special situations which were different from previous publications on ^{131}I in many respects : 1) the incidence of thyroid cancer was very high, espesially among children ; 2) the area around Chernobyl is iodine deficient ; 3) it was reported that various iodine prophylaxs were given. Therefore, ^{131}I could be the cause of thyroid cancer, and investigation on the dose-response relationship must be encouraged. Radiation by short-lived isotopes of iodine and tellurium, which may comprise a large percentage of the absorbed thyroid dose by inhalation may be more carcinogenic than ^{131}I and could be the cause thyroid cancers. External radiation by any type of isotopes as well as internal radiation can produce thyroid cancers.

Radiation to atomic bomb survivors was mainly external radiation at the time of the explosion of the atomic bomb, and the thyroid external radiation dose was estimated for each atomic survivor by the DS86 system. A large dose of external radiation induces hypothyroidism. However, it should be emphasized that thyroid cancer was induced in children by a low dose of medical external radiation (0.06 to 1.4 Gy) for enlarged thymus, tinea

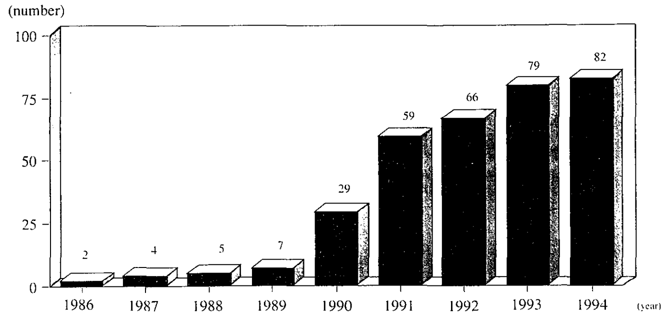

Fig. 4 Number of cases of childhood thyroid cancer in Belarus. (These data were obtained at the International Conference of Health Consequence of the Chernobyl and Radiological Accidents in November 20-23, 1995 Geneva, Switzerland)

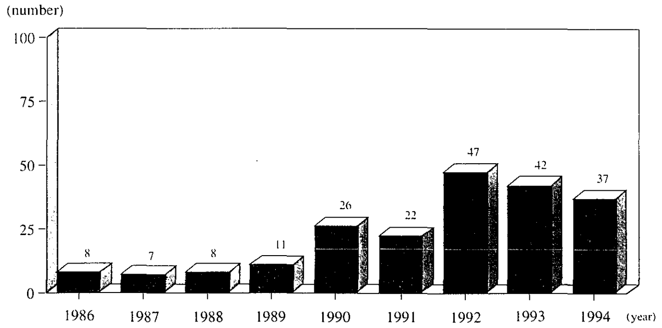

Fig. 5 Number of cases of childhood thyroid cancer in The Ukraine (These data were obtained at the International Conference of Health Consequence of the Chernobyl and Radiological Accidents in November 20-23, 1995 Geneva, Switzerland)

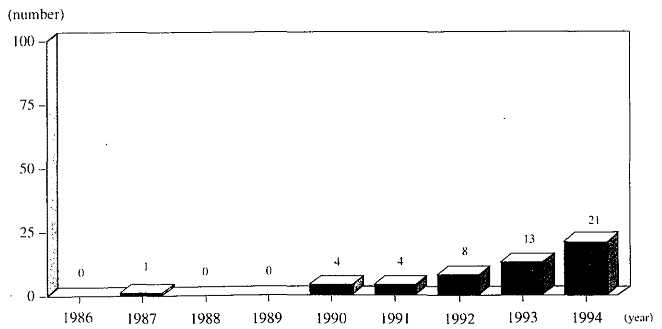

Fig. 6 Number of cases of childhood thyroid cancer in Russia. (These data were obtained at the International Conference of Health Consequence of the Chernobyl and Radiological Accidents in November 20-23, 1995 Geneva, Switzerland)

capitis, and skin hemangioma[30)31)32)33)34)]. Therefore, investigation on the relationship of external radiation and short-lived isotopes along with ^{131}I to thyroid cancers in children around Chernobyl may be important to elucidate the cause of thyroid cancers.

At the Nagasaki symposium held on June 1994, the need for international collaboration in the study of consequences to the thyroid of the Chernobyl accident was pointed out and an international steering committee has established, which was definitely a new step[35)]. Ten years have passed since the Chenobyl accident. A signifiant increase in autoimmune disease among atomic bomb survivors was demonstrated for 45 years after the atomic bomb explosion. We should recognize anew that we are still at the begining of the investigation of radiation-induced health consequences on not only thyroid disease but also on many other diseases such as leukemia, psychiatric disorders and so on after the Chernobyl accident.

Needless to say, anxienty among the inhabitants around Chernobyl regarding the effects of radiation are still strong, and are becoming storonger and storonger. Inconsistent and contradictory information is one of the causes of anxiety. Therefore, a long-term prospective study (case-control/cohort) should be conducted using an established diagnostic criteria and analyzed with an accurate estimation of exposure dose to external and/or internal radiation.

Finally, Nagasaki Symposium '95 Radiation and Human Health : proposal from Nagasaki was held on September 1995, in Nagasaki to commemorate the 50th anniversary of the atomic bombing[36)]. The speakers were invited from all over the world related to the nuclear events and realized that many Hibakusha (radiation exposued people) exist and distributed without any investigation or compensation. According to our experiences in Nagasaki and around Chernobyl, it is our duty to extend further our scientific knowledge for the international Hibakusha and to provede humanitarian aid as wall as from the medical care.

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