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The relationship of thyroid cancer in the people of the Marshall Islands to potential exposure to radioactive fallout from nuclear weapons testing

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INTRODUCTION

The United States nuclear weapons testing programme in the Pacific, conducted between 1946 and 1958 on Bikini and Enewetak atolls in the Marshall Islands, resulted in radioactive contamination of a number of neighbouring atolls. In that programme, a total of 66 nuclear tests were conducted. The potentially widespread exposure to radioactive iodines from nuclear fallout and subsequent publicity about adverse health effects has raised concerns about the risks of thyroid cancer and other thyroid disease in the Marshallese population.

The early fallout from the detonation of a hydrogen bomb on Bikini atoll on 1 March 1954 led to the most serious radiation exposures. It resulted in an average thyroid dose in a one-year-old child of 52 Gy on the downwind atoll Rongelap and 6.8 Gy on Utirik, an atoll further downwind (1). These exposed communities were provided with follow-up medical care over the decades since (2). The most frequent long-term health effect in the exposed population appeared to be an increased frequency of nodular thyroid disease including thyroid cancer (3).

A recent assessment by the Marshall Islands Nationwide Radiological Study has provided evidence that at least ten of the inhabited atolls or reef islands have been contaminated from the atmospheric explosions to various degrees (4-6). In conjunction with the Marshall Islands Nationwide Radiological Study we examined a large proportion of the Marshallese population potentially exposed to radioactive fallout for thyroid disease (7). We previously showed that thyroid nodules were very common, in particular in female Marshallese, and that the prevalence increased with age, but we found little evidence that benign thyroid nodules were related to exposure from nuclear fallout (8-10). In this report we explore the occurrence of thyroid cancer in this population and investigate this in relation to potential radio-iodine exposure, age, and sex.

METHODS

One objective of this study was to determine the prevalence of thyroid cancer in Marshallese people who lived anywhere in the Marshall Islands during the atomic bomb testing period, in particular in 1954, and thus were potentially exposed to fallout from the nuclear weapons tests. Between 1993 and 1997 we examined 7,221 Marshallese people for thyroid disease during four study clinical phases of work. 5,826 of this group were born before 1 January 1965 and were included in the epidemiological analysis reported here. Although the main population of interest were those alive during the testing period, we did not refuse anyone who requested an examination even if they were younger. Recruitment was by public announcement, through radio, and by word of mouth. Attendance was very high due to much publicity in recent years about health effects among Marshallese resulting in great concern about long-term effects of the bomb testing and about thyroid disease in particular. In the clinical phases, we examined 1,610 people in Ebeye (1993 and 1996), 5,263 people in Majuro (1994) and 348 people on some remote atolls (1997). Many residents of Ebeye and Majuro had previously lived on other atolls.

The thyroid screening programme was composed of two components: a personal interview and a clinical examination. Every participant who gave informed consent, after having been explained the background and the purpose of the study, was interviewed by a Marshallese assistant in his or her native language and underwent a medical examination by a medical team from Tohoku University School of Medicine. The interview consisted of questions relating to date of birth, residence history, reproductive history, general health and diet. The questionnaire inquired about atoll of residence for each year from birth to the year of interview. This information was cross-checked by asking for date and place of marriage and date and place of births of children of the study participants.

The clinical examination consisted of a medical examination of the thyroid by a physician including palpation of the neck and an ultrasound examination of the thyroid by a second physician using an ALOKA echo

camera SSD-121^{TM} with a 7.5 MHz mechanical sector probe. Both physicians were blinded to the results of the interview. For purposes of the examinations and our analysis, we defined a nodule as a focal abnormality of the echo pattern that was larger than 4 mm. All participants identified with a palpable nodule were further examined by a fine needle aspiration (FNA) biopsy of the dominant nodule.

Medical findings from biopsies were reported to individuals and health services. If a scar in the neck was found during the medical examination that indicated past thyroid surgery, we asked details of the surgery and then attempted to retrieve the histopathological report. If thyroid cancer was suspected on the basis of palpation and the FNA biopsy results, thyroid surgery was conducted in Majuro Hospital during a special visit by the physicians from the Tohoku University School of Medicine. Histopathological specimens from surgery were assessed in the Department of Pathology at Tohoku University Hospital. The medical monitoring has been described in detail elsewhere (8).

Three study populations were defined: those born before the Bravo test on 1 March 1954 (Bravo cohort), those born between 1 March 1954 and the end of the bomb test period (end-of-testing cohort), and those born between 1 March 1959 and 1 January 1965 (after testing cohort), the latter group to serve as unexposed control. The ‘end-of-testing’ cohort included people who were in-utero for more than three months at the end of the last atomic bomb detonation in August 1958 and thus were born before 1 March 1959. This, because the foetal thyroid actively concentrates iodine from the fourth month of gestation (11).

At present, no detailed assessment of individual radiation dose to the thyroid gland has been conducted for people in the Marshall Islands, other than for those exposed on Rongelap and Utirik from the Bravo test in 1954 (1), though we are presently pursuing those calculations. For the purposes of the analysis reported here, we derived a crude measure of thyroid dose for people residing on other atolls by adjusting dose estimates for people who were on Utirik (1) with environmental radiological data from each atoll recently collected and reported by Simon and Graham (4-6). We conveniently call this crude estimate a “Weighted Utirik dose”.

Dose estimates from the Bravo test on Utirik (1) were available for newborns and for persons 1, 6, 9, 12, 14 and 20 years old. The dose to newborns on Utirik was 59 cGy, 680 cGy to one-year-olds, decreased to 350 cGy in six-year-olds, and was an average of 165 cGy for people over age 20 (1). We derived dose estimates for other ages from age 1 onwards by fitting a fractional polynomial model (12) that allowed us to interpolate between ages. Unfortunately, we found it necessary to omit people exposed in the first year of life because dose estimates of this age group are highly uncertain due to lack of information on diet for quantifying exposure pathways. Maximum Cs-137 soil deposition levels for each atoll, as measured within the framework of the Nationwide Radiological Study of the Republic of the Marshall Islands, were reported to be most representative of the original deposition. Hence, we used those values to scale the dose from Utirik to other atolls (6). People who reported to be outside the Marshall Islands in 1954 were assumed unexposed.

The prevalence of thyroid cancer was described by histological type, age at diagnosis and according to study cohort, sex, and period of birth. Logistic regression analysis was used to model the probability of having thyroid cancer according to the weighted Utirik dose (quartiles), age at exposure (5 year age-bands), and sex. Analyses were carried out using the statistical programme Stata (13).

RESULTS

Our findings pertain specifically to 5,826 Marshallese that we examined between 1993 and 1997 and who were born before 1 January 1965. Among this group were 4,767 Marshallese born before the end of the testing period and thus potentially exposed, with 3,713 born before the Bravo detonation (Table 1). This group corresponds to 60-69% of the entire population at risk and who were still alive at the time of these examinations.

In our study sample we diagnosed 38 thyroid cancers, 28 of which were papillary carcinomas, 5 micropapillary carcinomas and 5 follicular carcinomas (table 2). In addition, we found 117 study participants who had scars that indicated previous surgery in the neck region. In 23 of these cases, the histopathological report stated the diagnosis of thyroid cancer. Among those were 16 papillary carcinomas, 3 micropapillary carcinomas, 1 follicular carcinoma, 1 mixed follicular/papillary carcinoma and two unspecified thyroid cancers. These 23 cases were operated between 1962 and 1992 with fifty percent operated after 1981. Our analysis of prevalence of thyroid cancer is based on a total of 61 cases of thyroid cancer (table 2). Histological reports of non-cancer cases frequently cited as adenomatous goitre (28), adenoma (12) and benign nodule (9). The majority of people were diagnosed between age 30 and 50 (table 2). For 38 previously operated people, the histopathological report could not be retrieved.

Study cohort	Males	Females	Total
Bravo*	1787	1926	3713
End-of-testing†	444	610	1054
After testing‡	443	616	1059
Total	2674	3152	5826

*Born before Bravo test on 1 March 1954 †Born between 1 March 1954 and 28 Feb 1959 ‡Born between 1 March 1960 and 1 January 1965

Table 1. Number of study participants by study cohort.

The prevalence of ever having had thyroid cancer was 1.1% in our entire study group. Thyroid cancer was more common among females, 1.2% versus 0.8% in males (table 3). The prevalence was highest in the Bravo cohort (1.4%) with a prevalence of 1.8% in females and 1.0% in males. There was no indication in this cohort that the prevalence was higher in the people who were exposed as children compared with those who were exposed as adults. Thyroid cancer was less common in the ‘end-of-testing’ and ‘after testing’ cohorts, indicating that the prevalence increased with age.

Weighted Utirik doses were derived for 3,390 people (91%) of the Bravo cohort. Forty-six people were omitted because they reported to have lived on the highly exposed atolls of Bikini, Enewetak or Rongelap in 1954, 82 people because they reported to have lived on multiple atolls or because their atoll of residence was not known, and 195 people because they were in the first year of life on March 1 1954 (see methods). Among those omitted people, five cases of thyroid cancer were known (two were on Rongelap at the time of the Bravo test, atoll of residence in 1954 was unknown for two, and one was under age 1 yr).

The weighted Utirik dose varied from 676 cGy in one-year-olds on Utirik at the time of Bravo, to virtually zero for all ages in Namorik, Lib and Jabwat where the Cs-137 deposition level did not exceed that from global fallout. Women in the third and fourth quartile of weighted Utirik dose had the highest prevalence, 2.0% and 2.5% respectively. The prevalence in the fourth quartile remained high (2.2%) even when we excluded the women who were exposed on Utirik. The probability of thyroid cancer appeared to increase with quartile of weighted Utirik dose in females, but not in males (figure 1).

In the regression model, subjects in the fourth quartile of weighted Utirik dose had a non-significant 1.9-fold increased risk of having had thyroid cancer compared to subjects in the lowest quartile of dose (table 4), though the increase was not significant. In addition, there was no evidence that sex modified the association between weighted Utirik dose and thyroid cancer. Females had a nearly two-fold higher risk of thyroid cancer than males ($p<0.05$). The risk of thyroid cancer generally increased with age, but the trend was not statistically significant.

Characteristic	Diagnoses from this work	Diagnosed prior	Total
Thyroid cancer histology			
Papillary	28	16	44
Micropapillary	5	3	8
Follicular	5	1	6
Follicular + papillary		1	1
Unspecified		2	2
*Age at diagnosis (years)**			
<30	1	3	4
30-39	8	10	18
40-49	12	7	19
50-59	8	2	10
60-69	6		6
70+	3		3
Not known		1	1
Total	38	23	61

*calculated on the basis of year of surgery for people diagnosed prior to the study

Table 2. Histology and age distribution of thyroid cancer.

Period of birth	Male (%)	Female (%)	Total (%)
Bravo cohort			
Before 1936	6/556	11/562	17/1118
(Adults in 1954)	(1.1%)	(2.0%)	(1.5%)
1936-1945	7/397	6/469	13/866
(Teenagers in 1954)	(1.8%)	(1.3%)	(1.5%)
1945-February 1954	4/834	17/895	21/1729
(Children in 1954)	(0.5%)	(1.9%)	(1.2%)
Total for Bravo cohort	17/1787	34/1926	51/3713
	(1.0%)	(1.8%)	(1.4%)
End-of-testing cohort	4/444	1/610	5/1054
(March 1954 -February 1959)	(0.9%)	(0.2%)	(0.5%)
After testing cohort	1/443	4/616	5/1059
(March 1959-January 1965)	(0.2%)	(0.7%)	(0.5%)
Total for the three cohorts	22/2674	39/3152	61/5826
	(0.8%)	(1.2%)	(1.1%)

Table 3. Prevalence of thyroid cancer by period of birth.

Factor	No. of cases of thyroid cancer (%)	No. of people	Adjusted odds ratio (95% CI)
Weighted Utirik dose (cGy)			
0—3.44	9 (1.1%)	848	1.00
3.45-7.50	10 (1.2%)	847	1.24 (0.48-3.18)
7.51—18.70	13 (1.5%)	848	1.58 (0.65-3.85)
18.71-676.66	14 (1.7%)	847	1.90 (0.78-4.62)
			χ^2 trend=2.34 p=0.13
Sex			
Male	15 (0.9%)	1637	1.00
Female	31 (1.8%)	1753	1.88 (1.01-3.50)*
Age at the time of Bravo (years)			
1-4.9	8 (1.0%)	836	1.00
5-9.9	11 (1.4%)	765	1.61 (0.64-4.09)
10-14.9	7 (1.4%)	490	1.68 (0.59-4.72)
15-19.9	8 (2.1%)	379	2.58 (0.94-7.10)
20+	12 (1.3%)	920	1.71 (0.67-4.38)
			χ^2 trend=1.53 p=0.22

*p-value<0.05

Table 4. Risk factors of thyroid cancer among 3,390 people alive at the Bravo test for whom a weighted Utirik dose could be derived.

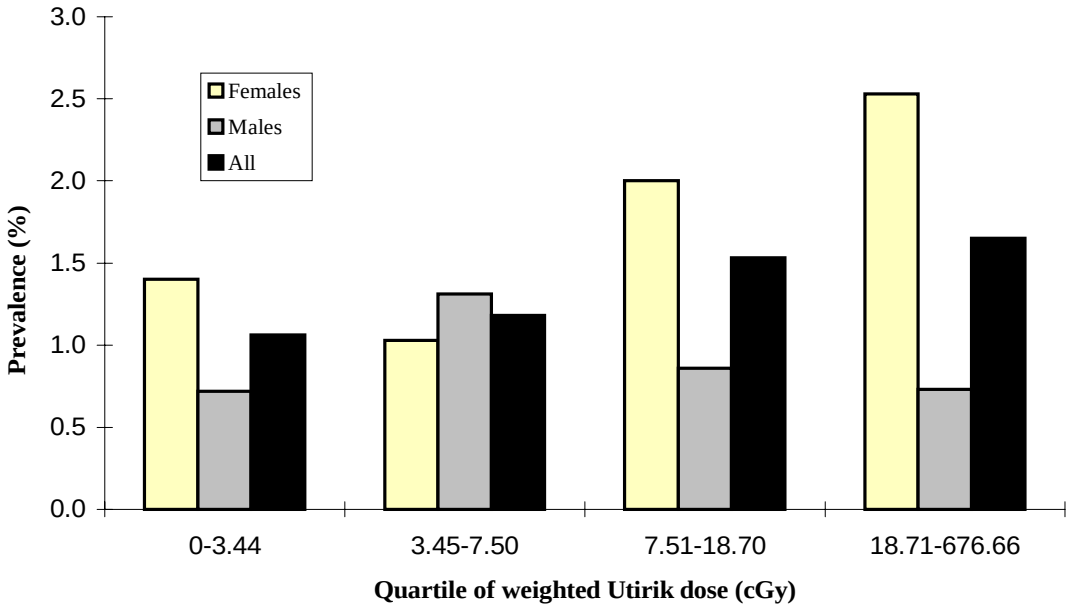

Figure 1. Thyroid cancer prevalence and weighted Utirik dose

DISCUSSION

The prevalence of thyroid cancer is high in the Marshall Islands. Among people we examined and who were alive at the time of the Bravo test, about one male and nearly two females per 100 residents were diagnosed with thyroid cancer or had been operated for thyroid cancer prior to our study. The prevalence is increased in subjects who were potentially exposed to radio-iodines from the atomic weapon testing programme, but is still 0.5% in people who were born afterwards. Previous research on radiation-induced thyroid cancer has documented an increasing risk of thyroid cancer with younger age at exposure (14-16). We did not find any evidence of any pronounced influence of age at exposure on thyroid cancer prevalence in our data.

The age distribution of papillary cancer in an unexposed American population showed that 60% of the patients were between age 30 to 59 years, with a peak at 43 years (17). Papillary cancer was more common among young people than among elderly; 15% of the patients were between 20 and 29 whereas only 5% of the patients were older than 70 years. That age distribution is very similar to that among the Marshallese described in Table 2. Our interpretation is that the thyroid cancers in the Marshallese population are likely to be a mixture of those that are radiation-induced and those that have occurred for other, unknown reasons (naturally occurring cancers). Moreover, since most thyroid cancers were diagnosed from a rather brief period of active screening, there is a strong link between age at exposure and age at diagnosis. This, together with the pronounced age dependence of thyroid cancer incidence could obscure any small increase of the prevalence of radiation-induced thyroid cancer at relatively young ages.

The prevalence of thyroid cancer in the Bravo cohort increased with quartile of weighted Utirik dose, though the test for trend was non-significant. The use of the crude dose estimates could have easily diluted any real trend of thyroid cancer prevalence with increasing thyroid dose in part, due to exposure misclassification. There is significant scope for improvement of this analysis by using more precise dosimetric estimates. The dose response relationship which we observed looks similar to that found during the follow-up investigations of the populations of Rongelap and Utirik (18). The incidence of papillary thyroid cancer was highest in the Rongelap and Alingnae population (5/86; 5.8%). In the less exposed Utirik population, it was 4/167 (2.4%), and in the presumably unexposed control population, it was 2/227 (0.9%). However, in our study, this dose response relationship was also seen among Marshallese people who were not on Rongelap or Utirik in 1954 at the time of the Bravo test.

The observed prevalence of ever having had thyroid cancer is also probably underestimated because we were unable to retrieve 38 histopathological reports of people who presented with a scar. If the distribution of diagnoses was the same as for people for whom the reports were retrieved, we could have missed 11 thyroid cancers in our study population. This missing data may introduce a bias since 13 of the missing 24 reports concerning study participants for whom a weighted Utirik dose could be calculated related to people in the lowest dose quartile. Since the conclusions of this study may be influenced considerably by the diagnosis of these 24

operated study participants, extra efforts need to be made to retrieve all missing pathology reports.

Susceptibility to thyroid cancer might be modified by genetic background. About 3-6% of the thyroid cancer cases in Europe and the USA show familial aggregation (19). Populations at higher risk include Moroccans and people with Jewish ancestry (20). The highest thyroid cancer incidence has been observed in Melanesians in New Caledonia (21). It still needs to be established whether Marshallese people are at increased risk because of genetic makeup. The other important modifier of thyroid cancer risk in the Marshall Islands is iodine deficiency. We reported that a moderate degree of iodine deficiency was found which might be responsible for some of the increased prevalence of thyroid nodules (9).

We made two important but limiting assumptions with our method of thyroid radiation dose estimation. First, we assumed that only the tests conducted in 1954, and in particular, the Bravo test, contributed to thyroid dose. There were 66 detonations over 13 years but 1954 was the most important year of the nuclear weapon testing programme since the Bravo detonation together with five other tests produced 45.0% of the total yield (equal to 107 MT equivalent TNT) from all tests during the programme (4). The Bravo test was also the only test that necessitated immediate evacuation of the people living in surrounding atolls. The second assumption was that observed Cs-137 soil deposition levels, resulting from all tests, were proportional to iodine transfer from the tests conducted in 1954.

The data presented here suggest a dose dependent increase of thyroid cancer prevalence among Marshallese who were living on other atolls than Rongelap and Utirik. To improve the certainty of this conclusion, individual thyroid dose reconstruction becomes an essential task for future work. This is by no means a simple undertaking since it has to consider pathways (5) which are very different from those modelled elsewhere, e.g. in the reconstruction of thyroid doses from the Chernobyl accident. With our planned dosimetric analysis, we will address several shortcomings of the current crude dose estimates, in particular, we can take into account the arrival times of the fallout (which determine the decay of short-lived radio-iodines) and incorporate exposures from tests in years other than in 1954.

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