Reprinted from the JAMA® Journal of the American Medical Association
August 7, 1987, Volume 258

Thyroid Neoplasia in Marshall Islanders Exposed to Nuclear Fallout

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We studied the risk of thyroid neoplasia in Marshall Islanders exposed to radioiodines in nuclear fallout from the 1954 BRAVO thermonuclear test. We screened 7266 Marshall Islanders for thyroid nodules; the islanders were from 14 atolls, including several southern atolls, which were the source of the best available unexposed comparison group. Using a retrospective cohort design, we determined the prevalence of thyroid nodularity in a subgroup of 2273 persons who were alive in 1954 and who therefore were potentially exposed to fallout from the BRAVO test. For those 12 atolls previously thought to be unexposed to fallout, the prevalence of thyroid nodules ranged from 0.9% to 10.6%. Using the distance of each atoll from the test site as a proxy for the radiation dose to the thyroid gland, a weighted linear regression showed an inverse linear relationship between distance and the age-adjusted prevalence of thyroid nodules. Distance was the strongest single predictor in logistic regression analysis. A new absolute risk estimate was calculated to be 1100 excess cases/Gy/y/1 $\times 10^6$ persons (11.0 excess cases/rad/y/1 million persons), 33% higher than previous estimates. We conclude that an excess of thyroid nodules was not limited only to the two northern atolls but extended throughout the northern atolls; this suggests a linear dose-response relationship.

(*JAMA* 1987;258:629-636)

IT HAS been 21 years since the publication of an early case series of thyroid neoplasia (including thyroid cancer and benign nodules) developing in children of Marshall Islanders as a late effect of exposure to radioactive fallout.[1] This exposure resulted from the detonation of a 15-megaton thermonuclear device on March 1, 1954, on Bikini Atoll in the northern Marshall Islands (Fig 1). This atmospheric nuclear test, code-named BRAVO, heavily contaminated the islands of Rongelap Atoll (86 inhabitants), and to a lesser extent, Utrik Atoll (167 inhabitants). The acute radiation sickness that developed in most of the people from Rongelap has been well described in previous reports.[2-15] The most common late effect from this exposure has been the development of thyroid nodules. Between 1954 and 1985, thyroid nodules developed in approximately 33% of the Rongelap population, including 63% of children less than 10 years old at the time of exposure, and 10% of the Utrik population.[2,16] Previous investigators have assumed that Rongelap and Utrik were the only two northern atolls exposed to fallout radiation; in their studies they used as unexposed controls those living on other northern atolls during the 1954 BRAVO test and found the prevalence of thyroid nodules in this comparison group to be 6.3%.[2,16] Although the estimates of thyroid dose for islanders from Rongelap and Utrik have been widely published, almost no information exists about the possible contamination of other northern atolls by radioiodines in 1954.[2,16,17] There is no verification that exposure to radioiodine did not occur on the other northern atolls.

Radiation exposure to the thyroid gland in the Marshallese people resulted primarily from beta radiation from a mixture of radioiodines (^{131}I, ^{132}I, ^{133}I, ^{135}I) and, to some extent, gamma radiation.[16,17] Knowledge about radiation-induced thyroid neoplasia comes largely from two sources: (1) studies of children exposed to gamma radiation for benign diseases[18-34] and (2) studies of survivors exposed to gamma radiation

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The opinions, conclusions, and proposals in this article are those of the authors and do not necessarily represent the views of the Robert Wood Johnson Foundation or the Marshall Islands Atomic Testing Litigation Project.

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at Hiroshima and Nagasaki.[35,36] Studies of exposures to iodine 131 in humans have been limited largely to ^{131}I therapy for patients with Graves' hyperthyroidism. It is unclear from these studies whether ^{131}I alone results in an excess of thyroid nodules.[37-41] Much less is known about the health risks of exposure to short-lived radioiodines other than ^{131}I. This information may be important in assessing the impact of radioiodine exposure from nuclear reactor accidents.

While the people from Rongelap and Utrik have been exhaustively studied during the last 33 years, these previous studies of thyroid neoplasia did not include the total geographical extent of the Republic of the Marshall Islands. To define more carefully the risk of thyroid neoplasia from nuclear fallout containing radioactive iodines, we conducted a retrospective cohort study of thyroid nodules in 7266 Marshallese people from 14 atolls, including several southern atolls, which served as the source of the best available unexposed comparison group.

METHODS

Study Hypothesis

The objectives of this study were as follows: (1) to determine the prevalence of thyroid nodules in people who were living on 14 northern and southern atolls at the time of the 1954 BRAVO detonation; (2) to test the null hypothesis that no difference existed in the prevalence of thyroid nodules among the 12 atolls of this study previously thought unexposed to radioactive fallout; and (3) if the null hypothesis is rejected, to determine which factors might explain the variation in rates of thyroid nodules.

Study Location

The Marshall Islands are located 2400 miles southwest of Hawaii; approximately 35 000 people (1985) live on 24 atolls spread among 375 000 square miles in the central Pacific Ocean. This population is distributed roughly in thirds on the following atolls: Majuro Atoll, the administrative district of the government of the Marshall Islands; Kwajalein Atoll; and the remaining 22 atolls, known collectively as the "outer islands." This study took place between June 1983 and March 1985 on 14 of the 24 inhabited atolls in the Marshall Islands (Fig 1).

For this study, northern atolls were defined as those north of Majuro (Rongelap, Utrik, Mejit Island, Ailuk, Likiep, Wotje, Maloelap, Kwajalein, Lae, Ujae, and Wotho), and southern atolls were defined as those south of Majuro (Jaluit, Ebon, and Mili). These 14 study atolls were selected to include all northern atolls that could have possibly been in the path of fallout and as many southern atolls as logistically feasible. Atolls that were not studied included five central atolls, two currently uninhabited northern atolls (Rongerik and Ailingnae), one southern atoll, and two atolls west of Bikini.

Study Design and Sample

A population-based retrospective cohort design was employed. Among the 7266 Marshallese people screened in this study, 2273 persons were alive in March 1954 and were residing on one of the 14 study atolls; they were, therefore, potentially exposed to the short-lived radioiodines. Since only these people were at risk for radioiodine-induced thyroid neoplasia, it is this group of 2273 persons that makes up the sample in this study.

During the course of this study, all residents (age 5 years and older) of each island selected for screening were invited and encouraged to receive thyroid examinations. Extensive discussions with traditional leaders of each atoll were conducted prior to each trip to ensure maximal communication to residents of each island. One to two weeks were spent on each atoll performing the screening examinations. The population of each atoll at the time of screening was estimated from the 1980 Marshall Islands census data.[42]

To offset the effect of self-selection by islanders of each atoll population, we attempted to screen the entire population of 13 primary atolls. Since migration out of the country is rare, the primary problem was capturing those members of the population, especially the population of 1954, who had moved to either of the two population centers, Majuro or Kwajalein. Screening programs were therefore conducted on Majuro and Kwajalein for those individuals and their families who had lived on any of the 13 northern or southern atolls in 1954. However, since we screened nearly a third of the population of Kwajalein Atoll for thyroid nodules, we also included Kwajalein as a primary atoll, making a total of 14 study atolls.

Exposure Criteria

Since the short-lived radioiodines (^{131}I, ^{132}I, ^{133}I, ^{135}I) all have half-lives of less than eight days, the bulk of the radioiodine exposure from the BRAVO event occurred during the month of March 1954. Therefore, the most important historical information concerning the radioiodine dose was the location of residence in March 1954. Because most individuals can provide vivid descriptions of what they were doing during the dramatic BRAVO test, the question was posed in the following manner: "Where were you living when the 'bomb' caused the Rongelap and Utrik people to be moved from their homeland?" Individuals born after March 1, 1954, but before Dec 31, 1954, were classified as in utero at the time of the blast, and their atoll of residence in 1954 was classified according to their atoll of birth. Because of the relative proximity of all the islands within each atoll and the long distance between any atoll and the blast site, all individuals from different islands within an atoll were classified by the atoll name for the purposes of 1954 residence status.

Table 1.—Distance and Direction of Study Atolls From Bikini Atoll

Atoll	Distance, Miles*	θ, °†
Rongelap	120	20
Utrik	321	6
Mejit Island‡	398	15
Ailuk	342	18
Likiep	308	26
Wotje	376	25
Maloelap	460	28
Lae	198	71
Ujae	187	80
Wotho	112	64
Kwajalein	192	51
Jaluit	500	54
Ebon	538	64
Mili	589	42

*Distance from atoll to BRAVO test site on Bikini Atoll in statute miles.
†Angle of atoll from 0° latitude line drawn through Bikini Atoll.
‡Mejit Island is classified as an atoll for the purposes of this study.

Since the people live on small land masses, the atolls represent discrete points in the vast ocean area of the Marshall Islands. The distance from each atoll to the site of the 1954 BRAVO test (Bikini Atoll) was therefore selected as a proxy for the radioiodine dose received in 1954.

A second variable was developed to better characterize the exposure status of the Marshallese people. A directional variable, θ, was selected as a proxy for meteorologic conditions, such as wind and precipitation, that may have influenced the distribution of the fallout cloud. We defined θ as the angle in degrees, measured clockwise, of each of the 14 atolls from a 0° latitude line drawn through Bikini Atoll, using Bikini as the vertex. Table 1 shows the distance of each atoll from the BRAVO test site as well as the angle θ of each atoll from an east-west line drawn through Bikini.

Diagnostic Criteria

We defined a thyroid nodule as one that was palpable, discrete, and estimated to be 1.0 cm or greater. Findings of indiscrete or uncertain lesions and

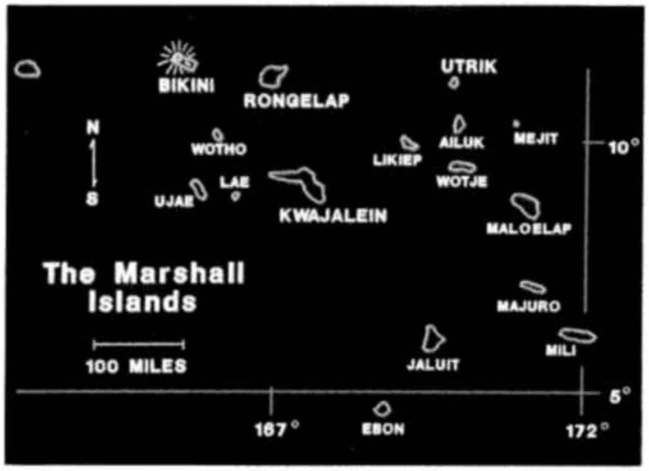

Fig 1.—Marshall Islands. BRAVO test site is shown on Bikini Atoll. People on other atolls were screened for thyroid nodules.

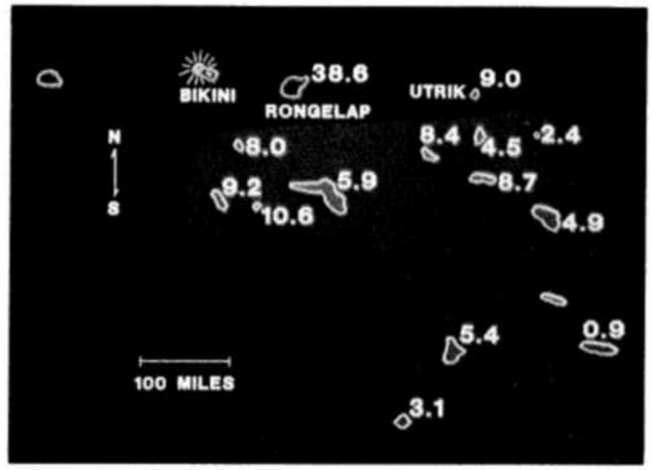

Fig 2.—Prevalence of thyroid nodules. Atolls shown in color inset were previously assumed unexposed to radioiodine from nuclear fallout.

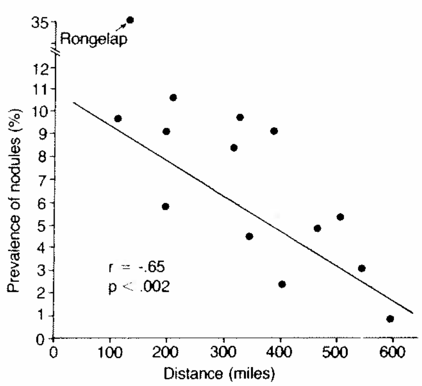

Fig 3.—Weighted linear regression. Age-adjusted prevalence of thyroid nodules weighted by inverse of population variance is plotted against distance from BRAVO test on Bikini Atoll.

Table 2.—Proportions of Atoll Populations Screened for Thyroid Nodularity

Atoll	Estimated Population*	Total No. (%) Screened
Rongelap	201	122 (61)
Utrik	287	184 (64)
Mejit Island	278	263 (95)
Ailuk	353	217 (61)
Likiep	419	137 (33)
Wotje	466	364 (78)
Maloelap	534	443 (83)
Lae	206	149 (72)
Ujae	269	187 (70)
Wotho	74	34 (46)
Jaluit	1295	759 (59)
Ebon	792	517 (65)
Mili	681	319 (47)
Subtotal	**5855**	**3735 (64)**
Majuro†	10 791	1723 (16)
Kwajalein†	6061	1808 (30)
Total	**22 707**	**7266 (32)**

*Projected from 1980 Marshall Islands census data.[42]

†Screening of the entire Kwajalein and Majuro populations was not attempted; only persons from these two atolls who had lived on the other 13 primary atolls in 1954 were screened.

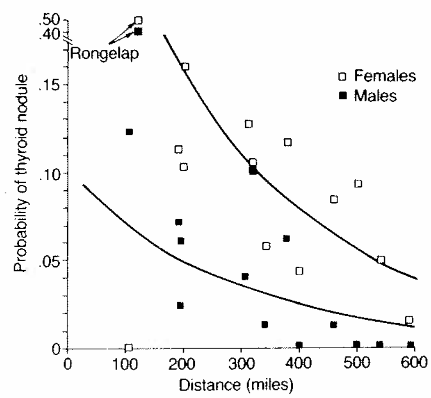

Fig 4.—Logistic regression analysis. Probability of thyroid nodule developing in an individual (from fitted logistic model) is shown for each sex, given mean age, as function of distance from Bikini Atoll. Actual prevalence data are also plotted. Females, top curve, and males, bottom curve.

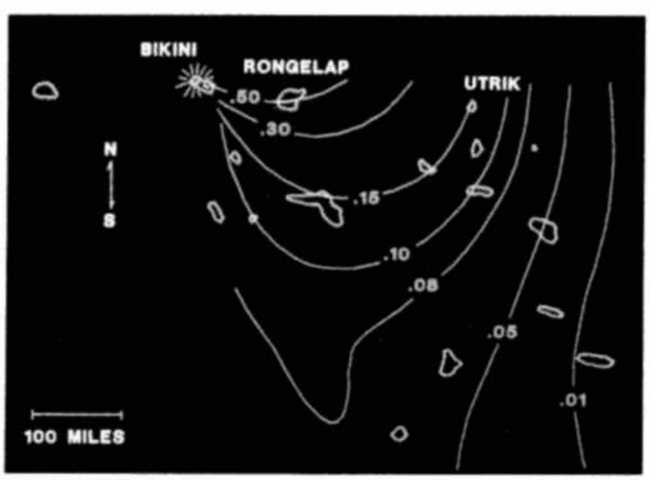

Fig 5.—Probability contours. Graph shows fitted probability contours for thyroid nodules for females, computed from complete logistic model. Distance was calculated for each contour of fixed probability, given mean age of females, for values of θ from 0° to 80°.

Table 3.—Descriptive Statistics of 1954 Cohort and Prevalence of Thyroid Nodularity

Atoll of Residence	Persons Alive in 1954	Mean Age, y	Females, %	Solitary Nodules	Previous Thyroidectomy*	Total Nodules	Crude Prevalence, %	Age-Adjusted Prevalence, %
Rongelap	44	45.9	54.5	0	17	17	38.6	37.2
Utrik	67	47.4	56.7	1	5	6	9.0	10.3
Mejit Island	167	46.2	54.8	3	1	4	2.4	2.4
Ailuk	177	45.6	58.0	7	1	8	4.5	4.9
Likiep	167	47.7	53.8	12	2	14	8.4	8.7
Wotje	161	47.8	48.7	9	5	14	8.7	9.6
Maloelap	183	46.5	53.5	7	2	9	4.9	4.7
Lae	66	48.4	48.4	6	1	7	10.6	10.2
Ujae	108	46.5	59.6	7	3	10	9.3	9.6
Wotho	25	44.8	66.7	1	1	2	8.0	9.8
Kwajalein	425	51.4	49.8	13	12	25	5.9	5.3
Jaluit	313	48.6	59.2	15	2	17	5.4	5.2
Ebon	259	45.4	60.1	5	3	8	3.1	3.2
Mili	111	47.2	55.6	1	0	1	0.9	0.8
Total	**2273**	48.8	55.0	**87**	**55**	**142**	6.2	5.7

*Excludes five subjects in whom the pathologic findings indicated normal thyroid disease.

Table 4.—Predictors of Risk for Thyroid Nodules

	Logistic Regression Analysis		
Variable	Regression Coefficient	SE	Odds Ratio (95% Confidence Intervals)
Constant	−1.872	0.8310	. . .
Age	0.01914*	0.0062	1.21/10 y (1.07/10 y − 1.37/10 y)
Sex†	1.313‡	0.2180	3.72 F/M (2.42 − 5.70 F/M)
Distance	−0.01098‡	0.0021	0.33/100 miles (0.22/100 miles − 0.50/100 miles)
θ	−0.05312‡	0.0132	0.59/10° (0.45/10° − 0.76/10°)
Distance × θ	0.0001457‡	0.00004	1.16/100 miles × 10° (1.07/100 miles × 10°-1.25/100 miles × 10°)

*$P = .003$.
†Male = 1 and female = 2.
‡$P < .001$.

nodules less than 1 cm were classified as normal thyroid examination results. The term *thyroid nodule* does not connote the histologic characteristics of a lesion. We use the terms *thyroid neoplasia* and *thyroid nodule* synonymously in this article to indicate that such lesions may be either malignant or benign.

Because the hypothesis of this study pertains strictly to solitary thyroid nodules, individuals with Graves' disease, multinodular goiter, or simple diffuse goiter were not classified as having nodules for the purpose of this analysis. Individuals whose 1954 residence was not one of the 14 study atolls were excluded altogether from the prevalence data.

Previous Thyroidectomy

Almost all individuals from Rongelap and Utrik in whom thyroid nodules developed had had thyroid surgery, generally in the United States under the direction of Brookhaven National Laboratory, Upton, NY.[2] This is also true for certain individuals in the comparison groups. The majority of the atoll populations, however, had had little access to physicians. As a result, most thyroid nodules in this study were newly diagnosed. Because cohort attrition from thyroid mortality is extremely low and because nodules generally do not spontaneously regress, we decided to count individuals with previous thyroidectomy as having had a thyroid nodule if the indication for surgery was the removal of a thyroid nodule. For Marshall Islanders with prior thyroidectomy, the indication for the surgery was ascertained from available medical records. The histologic characteristics of these malignant and benign neoplasms have been described previously.[2] Individuals with previous thyroid surgery for Graves' disease, simple goiter, or indications other than a thyroid nodule were not classified as having a thyroid nodule in this analysis. Individuals whose surgical histologic findings were "normal thyroid tissue" were also not classified as having nodules. The net result of these classifications is that the prevalence data reported here are thought to approximate closely the cumulative incidence of thyroid nodularity since 1954.

Thyroid Carcinoma

The prevalence of solitary thyroid nodules was the outcome variable in this study. Because many individuals with new thyroid nodules were treated medically rather than referred for surgery, ascertainment of thyroid carcinoma was incomplete in this study cohort. However, since previous authors have provided absolute risk estimates for total thyroid nodules as well as for thyroid carcinoma, our risk estimates for total thyroid nodules in this study can be directly compared.[16]

Data Collection

A physical examination of the thyroid gland was carefully performed by one of us (T.E.H.) on all 7266 study participants. Detailed drawings and explanations were recorded for all thyroid abnormalities, including evidence of previous thyroid surgery. Nodules were described by location, consistency, contour, discreteness, and size. In addition to demographic information the following information was also obtained: a brief medical and surgical history, blood pressure, pulse, and examination of the cervical lymph nodes. Residence location in 1954 was recorded. Persons with thyroid abnormalities were referred for a comprehensive medical evaluation in the author's (T.E.H.) central office on Majuro Atoll.

The same qualified Marshallese interpreter was present at all screening examinations. Travel to the 14 atolls and islands within atolls was accomplished by airplane, ship, small craft, and outrigger canoe.

To diminish observer bias, the thyroid examiner was masked to the history of exposure: the Marshallese interpreter asked each person about his or her 1954 residence in their native language. Individuals who were too young to remember the 1954 thermonuclear BRAVO test were asked where they were born, and their residence history for their first five years was noted.

Risk Assessment

The absolute risk coefficient for thyroid neoplasia is expressed as the number of excess nodules/thyroid dose/years at risk/1 million persons, where excess nodules are the observed minus expected nodules and the thyroid dose is expressed in grays (1 Gy = 100 rad). The most recent estimates for the mean dose of radiation to the thyroid gland in Marshall Islanders are 21 Gy (2100 rad) for Rongelap Islanders and 2.80 Gy (280 rad) for Utrik Islanders.[16] To calculate a single absolute risk coefficient for both of these populations, previous studies used the following information: a mean thyroid dose of 8 Gy (800 rad), the mean number of years at risk (18), the observed number of nodules (46), and the expected number of nodules (16) for the combined population of 251 Rongelap and Utrik Islanders. The calculation for the expected number of nodules was based on a prevalence of 6.3% for atolls assumed unexposed to fallout.[16]

We determined a new value for the prevalence of nodules in unexposed Marshall Islanders. To calculate a new absolute risk coefficient, we used the expected number of nodules determined with this new prevalence value as well as the above information concerning mean dose, mean years at risk, and observed nodules for the original 251 Rongelap and Utrik Islanders.

Internal Validity

Since all thyroid examinations were performed by a single investigator (T.E.H.), it was important to validate these observations. A substudy was designed that compared, in a masked fashion, results of the author's physical examination of the thyroid gland with results of the physical examination by an expert in thyroid disease. A group of 173 individuals whom the author had examined during the previous two years was asked to participate in this study. Approximately 50% of these individuals had previously had normal thyroid examination results and were randomly selected from northern and southern atolls. The remaining 50% had nodular thyroid abnormalities. Each of the 173 people was examined separately by an experienced thyroid examiner from the University of Washington, Seattle. The second examiner had no prior knowledge of the author's previous examinations. In addition, Dr Hamilton repeated examination of any individual (masked to his previous examination) when there was disagreement between his results and those of the visiting thyroid examiner. Approximately 95% of this 173-person cohort complied with these examinations. Excellent agreement was obtained between the two examiners (87% observed agreement, kappa = .80).

RESULTS

Demographic Characteristics of Cohort

A mean of 64% of the populations of the 13 primary atolls was screened, with a range of 33% to 95% (Table 2). As discussed in the "Methods" section, selected screening examinations were performed on Majuro and Kwajalein atolls to find those individuals who had lived on any of the 13 primary atolls at the time of the 1954 BRAVO test. Because nearly a third of Kwajalein Atoll was screened, it was added to the other 13 primary atolls for the subsequent analyses, making a total of 14 study atolls.

Prevalence of Thyroid Nodularity

Of the 7266 persons screened, 2273 were alive at the time of the BRAVO test and were residing on one of the 14 study atolls on March 1, 1954 (Table 3). Exposure to the short-lived radioiodines ^{131}I, ^{132}I, ^{133}I, and ^{135}I was therefore possible in this group. Since these isotopes have half-lives of eight days or less, exposure to radioiodines from the BRAVO test fallout was not possible in persons born after 1954.

The numbers of people with solitary thyroid nodules (mean estimated size, 2.1 cm), previous thyroidectomy for a thyroid nodule, total thyroid nodules, and the prevalence of thyroid nodules for the reconstructed 1954 population appear in Table 3. For the 12 atolls previously thought unexposed to fallout radiation, the prevalence of nodules ranged from 0.9% to 10.6% (Fig 2). If these atolls were not exposed to radioiodines from the BRAVO test, we would expect, in the absence of other risk factors for thyroid nodularity, to see the same prevalence of thyroid nodules in all the atolls. To test this hypothesis, we performed a χ^2 analysis. The results reject the null hypothesis that no difference exists in the prevalence of thyroid nodules among these 12 atolls ($\chi^2 = 23.45$, $df = 11$, $P < .025$).

Predictors of Risk for Thyroid Neoplasia

To better understand the wide variation in rates of thyroid nodules, we performed multivariate analysis. Since thyroid dose estimates for people living on these 12 atolls are lacking, the distance of each atoll from the Bikini test site was selected as a proxy for the dose of radioiodine received by the thyroid gland. Weighted linear regression using the age-adjusted prevalence of nodules by atoll of residence in 1954 as the dependent variable shows a highly significant inverse linear relationship with distance from Bikini ($r = -.65$, $P < .002$) (Fig 3). Although northern atolls used in previous studies as a source for unexposed controls were found to have a prevalence of thyroid nodules of 6.3%,[2,16] the prevalence of nodules in our study continues to decrease to less than 1% as the distance from the site of the BRAVO test increases. We believe a better estimate for the prevalence of thyroid nodules in unexposed Marshallese to be 2.45%, the mean prevalence of the two southernmost atolls.

To examine risk at the level of the individual, we used logistic regression analysis, in which the presence or absence of a thyroid nodule was the dependent variable. Not only distance but also age and sex, θ (the angle from 0° latitude), and the product of θ and distance were all significant contributors to the logistic model (Table 4). The addition of inverse distance terms or higher order polynomial distance terms was not significant.

The odds ratios obtained from the regression coefficients show that the probability of a thyroid nodule developing in a female is 3.7 times higher than that in males (Table 4), a finding consistent with those of other studies of thyroid exposure.[40]

The odds ratio for distance is 0.33 per 100 miles from the test site, and for θ, 0.59 for every 10°. In other words, the probability of a nodule decreases approximately threefold for every 100 miles farther from Bikini and twofold for every 10° going east to west in a clockwise direction. Figure 4 shows the fitted logistic model for males and females, given mean age, with the actual prevalence data plotted. Again, as seen with linear regression, the probability decreases as the distance from Bikini increases.

To better illustrate the interaction of distance and θ, we developed a set of probability contours on the map of the Marshall Islands using the logistic model with all five variables. We set the variable sex equal to females and the variable age equal to the mean age of females. For each of seven fixed probabilities between .5 and .01, the distance was calculated for possible values of θ. The values of θ selected were between 0°

and 80°, which bounds the area of this study. As shown in Fig 5, these probability contours illustrate that the chance of developing thyroid nodules is influenced by both distance and θ in a variable manner. For example, for a fixed distance of 300 miles from Bikini, the probability decreases as θ increases. However, for most fixed distances greater than 400 miles from the test site, the probability increases with θ. These results are consistent with previously published fallout patterns showing an initial eastern pathway of the BRAVO fallout cloud.[43] They are also consistent with a computer simulation pattern that suggested that after a predominantly eastern direction, toward Utrik, the fallout cloud moved south and west from Utrik.[44]

Absolute Risk Assessment

The absolute risk coefficient has been used to compare the risk for thyroid nodules among exposed populations[45] and can be expressed as follows: absolute risk coefficient = number of excess cases/Gy/years at risk/1 × 10⁶ persons (number of excess cases/rad/years at risk/1 million persons), where number of excess cases is the number of observed nodules minus the number expected. Using a prevalence of nodules of 2.45% determined in this study for unexposed Marshallese, we determined a new absolute risk coefficient for the Rongelap and Utrik people exposed to radioactive iodines. Since estimates of the thyroid dose and years at risk for these populations were known from previous studies (see "Methods" section), we calculated a new risk coefficient of 1100 excess cases/Gy/y/1 × 10^6 persons (11.0 excess cases/rad/y/1 million persons).

COMMENT

This study demonstrates a strong inverse linear relationship between the probability of thyroid nodules developing in Marshall Islanders and the distance of their 1954 home atoll from the Bikini test site. The direction of each atoll relative to Bikini was also an important risk factor. Our results indicate that excess thyroid nodules in Marshall Islanders were not limited to the two northern atolls of Rongelap and Utrik but occurred throughout many of the Marshall Islands. These findings suggest that the geographic extent of radioiodine exposure from the 1954 BRAVO test was much broader than previously assumed.

Without thyroid dose estimates for people living on 12 of the 14 atolls in this study, radiation exposure cannot be proved as the cause of these neoplasms. Other risk factors for thyroid neoplasia, however, do not appear to be present. There is no evidence for iodine deficiency in this population: the diet of the Marshallese population is well known to have ample iodine content, especially on the outer islands, where the diet is high in fresh fish.[2,3] In contrast to the United States, no head and neck irradiation of Marshallese children was employed as therapy for benign diseases of childhood such as acne, presumed tonsilar or thymic enlargement, cervical adenitis, or fungal infections of the scalp. There are no known dietary or environmental goitrogens that are used in the Marshall Islands. If other unknown risk factors for thyroid disease are present in this population, it must be postulated that they exert their effects in a pattern such that the risk from exposure decreases with distance from Bikini Atoll. Thus, the absence of other known risk factors for thyroid nodularity and the presence of a strong inverse linear relationship between thyroid nodularity and the distance of each atoll from the BRAVO test site suggest radioactive fallout as the most likely cause of these neoplasms.

Although authors of previous clinical studies of Marshall Islanders assumed that 12 of the 14 atolls in this study were unexposed, other environmental assessment studies reported evidence that suggests that fallout contamination was not limited to Rongelap and Utrik. Robison and colleagues[46] reported that several inhabited atolls other than Rongelap and Utrik contained low levels of long-lived radionuclides that were likely residual from intermediate-range fallout in the Marshall Islands. Although the dose extrapolations from 1978 to 1954 were not done for these atolls, the low doses received from the longer-lived isotopes, such as cesium 137 and strontium 90, would not have contributed significantly to the thyroid dose during these years.

An additional report documented a gamma dose at Ailuk Atoll to be 0.01 Gy/h (1.0 rad/h) one hour after the BRAVO detonation;[43] such data suggest that this atoll, previously thought to be unexposed, received fallout. A computer simulation of the fallout cloud utilizing all available meteorologic data predicted that after an initial eastern direction, the maximal point of radiation 16 hours after the detonation would have been midway between Rongelap and Kwajalein.[44] This suggests that the fallout cloud may have shifted from an initial eastern path to a south or southwest direction. This simulation model is consistent with the results of our study, which show that, except for Rongelap, the prevalence of thyroid nodules was highest in this region on the atolls of Lae, Ujae, Wotho, and Likiep (Fig 2).

The thyroid doses of people living on atolls previously assumed to be free from exposure to radioactive fallout may have been affected by long exposure times. While people on Rongelap and Utrik were evacuated 48 to 72 hours after detonation, no such evacuation took place on other atolls.[47] Thus, people on those atolls may have had lower peak exposures than on Utrik, but because of continued exposure for the entire decay process of the radioiodines, their cumulative thyroid doses may have been as high as or higher than those on Utrik.

One methodologic advantage afforded by the Marshall Islands is that the geography of these islands has provided considerable variation on our proxy for exposure. While the thyroid doses for persons on these atolls is not known, the position of small land masses across thousands of square miles of ocean permits us to know the distance from the blast site exactly. Second, residents of these atolls could not easily move from atoll to atoll in short periods of time, especially in 1954, making it possible to ascertain on which atolls persons were living during the exposure period of the BRAVO test. These factors may in part explain why the variables distance and θ appear to be such strong proxies for radiation dose or conditions that affected the dose.

This study has several limitations that deserve mention. The ascertainment of exposure, which involves reports from participants, is subject to recall bias, especially in cultures such as the Marshall Islands that are not time oriented. Asking the question in terms of where one lived in March 1954 might yield answers of questionable accuracy. However, persons in this study were asked where they lived when the "bomb" exploded, causing the Rongelap and Utrik people to be evacuated from their homeland. The detonation of the BRAVO hydrogen test was a dramatic event: people on many atolls in the northern Marshalls could see the light, feel the blast, and see the fallout on vegetation hours after the blast. In much the same way as people recall clearly what they were doing at the time of Pearl Harbor or the assassination of John F. Kennedy, this dramatic hydrogen bomb affected the Marshallese people in a way such that they could provide vivid descriptions of what they were doing and where they were living in 1954 at the time of the test. For individuals living on southern atolls who could not see the blast, some misclassification of exposure status is possible, since they would not have had the personal experience of this dramatic event to date their 1954 atoll of residence. However, if such persons incorrectly recalled their location in 1954, the error would have probably been another southern atoll, since they would likely have remembered the BRAVO test had they lived on a northern atoll. In addition, transportation to and from these islands in the 1950s was not frequent, so the likelihood of misclassifying exposure remains small.

The issue of multiple exposures arises in this study population since there were 66 announced nuclear tests in the Marshall Islands between 1946 and 1958.[43] Many of these tests,[43] however, took place on Eniwetok Atoll, which is located about 200 miles west of Bikini. In addition, most of these tests were conducted when the prevailing winds were heading away from the Marshall Islands. More importantly, the BRAVO test was the largest of the 66 nuclear tests; it is the only test that people on distant atolls recall having seen. Thus, while it is possible that atolls close to Bikini, such as Rongelap, may have been exposed on multiple occasions, it is unlikely that such exposure occurred on distant atolls.

Because this study was a retrospective cohort design, the important issue of latency cannot be addressed. Prospective studies of the Rongelap and Utrik populations reported a mean latency for thyroid nodules of 13 years for Rongelap children exposed at ages less than 10 years.[16] The Utrik children, with lower thyroid doses, had a mean latency of 25 years. Whether persons exposed to smaller doses in the present study may exhibit even longer latent periods is unknown. Since latent periods at least as long as 34 years are thought to exist in other populations exposed to thyroid irradiation,[22,33] it will be necessary to continue close follow-up of this population.

The results of this study suggest that the northern atolls used in previous studies as a source for unexposed controls, with a prevalence of nodules of 6.3%, were inappropriately selected, since the prevalence in our study continues to decrease to less than 1% for the southern atolls, which are located the farthest from the Bikini test site. We believe that a better estimate of the prevalence of thyroid nodules in unexposed Marshallese is 2.45%, the mean prevalence of the two southernmost atolls. Since the prevalence continues to decrease to a value less than 1% for the atoll farthest from the blast site, 2.45% is probably a conservative estimate for the spontaneous or background rate of solitary thyroid nodules in the Marshall Islands.

Because authors of previous studies used the prevalence of 6.3% for presumably unexposed controls, their risk coefficient of 830 excess cases/Gy/y/1×10^6 persons (8.3 excess cases/rad/y/1 million persons)[16] underestimates the true risk. Using our estimate of 2.45% for the prevalence of nodules in unexposed Marshallese, our new risk coefficient is 1100 excess cases/Gy/y/1×10^6 persons (11.0 excess cases/rad/y/1 million persons). This is 33% higher than the previous estimate and is quite close to a published composite estimate of 12.3 (1230) for gamma radiation.[32]

The components of radiation dose to the thyroid gland in Marshall Islanders exposed to fallout are relatively unique among studies of humans in whom thyroid neoplasia has developed from ionizing radiation. While gamma radiation accounts for part of the total thyroid dose in the Marshall Islands exposure (4% to 16%), the majority of the thyroid dose came from the short-lived radioiodines, ^{132}I, ^{133}I, and ^{135}I, and, to a lesser extent, ^{131}I.[16] There is little information in the literature, other than that from exposures in the Marshall Islands, concerning the effects of these radioiodines in humans. Although ^{131}I alone is known to induce thyroid neoplasms in animal studies,[48,49] it is much less effective in the induction of human thyroid neoplasms, possibly 50 times less so than gamma irradiation.[32] Indeed, studies of ^{131}I therapy in Graves' disease have led to doubts about whether ^{131}I alone induces thyroid nodules in humans.[37-41,50] One explanation for the ineffectiveness of ^{131}I as a carcinogen in these studies may be that autoimmune thyroid disease renders the thyroid gland resistant to the development of neoplasms from ^{131}I irradiation. An additional factor is the nonuniform distribution of ^{131}I within thyroid tissue compared with gamma radiation; the dose from this type of distribution can ablate tissue at localized "hot spots" and result in a lower dose to the remaining thyroid tissue. Other explanations include the lower dose rate of beta-emitting ^{131}I compared with gamma radiation and the decreased potential of the thyroid gland to undergo malignant transformation once ablative doses of ^{131}I have been received by the entire gland.[40] However, while the role of ^{131}I as an inducer of thyroid neoplasia remains controversial, it should be emphasized that radioiodine fallout contains not only ^{131}I but a mixture of short-lived, higher-energy radioiodines.

The public health implications of these results are important not only to the Marshallese people but also to populations that may be exposed to short-lived radioiodines from fallout such as may occur during nuclear reactor accidents. These isotopes include the higher energy beta-emitters ^{132}I, ^{133}I, and ^{135}I and do appear to be effective inducers of thyroid nodules. In our study, we found the absolute risk coefficient to be nearly identical to the estimate for gamma irradiation. Thus, populations exposed to radioiodine fallout should not only be considered for potassium iodide prophylaxis at the time of contamination but should also be carefully followed up for the late development of thyroid nodules. We anticipate the expected rates of such neoplasms to be similar to those found from gamma radiation.

The field work for this study was supported by the Marshall Islands Atomic Testing Litigation Project, Los Angeles. The analysis and preparation of this manuscript was supported in part by a grant from the Robert Wood Johnson Foundation, Princeton, NJ.

We are indebted to the following Marshallese field staff: Staff Director Atra Lang, Leilani Lokboj, Julie Lloyd, Winnie MacQuinn, Aida Nashion, Anibar Timothy, and Lijon Eknilang. Special gratitude is expressed for the cooperation of the people of the Marshall Islands, the local council governments on the atolls, Minister of Health Dr Jeton Anjain (1982), representatives of the Republic of the Marshall Islands, and to all members of the Marshall Islands Atomic Testing Litigation Project. We are also indebted to Robert Griep, MD, and Lori Bernstein for participation in the validation aspects of this study; to Bruce Psaty, MD, MPH, Tom Koepsell, MD, MPH, and Linda Rosenstock, MD, MPH, for critical review of the manuscript; to Mary Miller for assistance in data abstraction; and to Paulette Gilliam for preparation of the manuscript.

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