Thyroid Nodularity and Chromosome Aberrations Among Women in Areas of High Background Radiation in China

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Thyroid nodularity following continuous low-dose radiation exposure in China was determined in 1,001 women aged 50–65 years who resided in areas of high background radiation (330 mR/yr) their entire lives, and in 1,005 comparison subjects exposed to normal levels of radiation (114 mR/yr). Cumulative doses to the thyroid were estimated to be of the order of 14 cGy and 5 cGy, respectively. Personal interviews and physical examinations were conducted, and measurements were made of serum thyroid hormone levels, urinary iodine concentrations, and chromosome aberrations in circulating lymphocytes. For all nodular disease, the prevalences in the high background and control areas were 9.5% and 9.3%, respectively. For single nodules, the prevalences were 7.4% in the high background area and 6.6% in the control area (prevalence ratio = 1.13; 95% confidence interval = 0.82–1.55). There were no differences found in serum levels of thyroid hormones. Women in the high background region, however, had significantly lower concentrations of urinary iodine and significantly higher frequencies of stable and unstable chromosome aberrations. Increased intake of allium vegetables such as garlic and onions was associated with a decreased risk of nodular disease, which seems consistent with experimental studies suggesting that allium compounds can inhibit tumor growth and proliferation. The prevalence of mild diffuse goiter was higher in the high background radiation region, perhaps related to a low dietary intake of iodine. These data suggest that continuous exposure to low-level radiation throughout life is unlikely to appreciably increase the risk of thyroid cancer. However, such exposure may cause chromosomal damage. [J Natl Cancer Inst 82:478–485, 1990]

Ionizing radiation is known to cause both benign and malignant thyroid nodules (*1–7*), but the potential hazard from low-dose exposures delivered over many years has not been thoroughly evaluated. Thyroid cancer is of particular importance in radiation biology because, with the possible exception of leukemia following fetal exposure, it is the only cancer linked to significant increases in risk at doses below 10 cGy (*7*). Its risk coefficient (excess cancers per unit population dose) is among the highest of all cancers, and the continuing scientific controversy over the magnitude of low-dose effects (*8*) gives the study of radiogenic thyroid cancer special significance. Women living in areas of high background radiation represent an appropriate population for study because they are continuously exposed to low levels throughout life, including childhood and adolescence, when the thyroid appears most sensitive to the damaging effects of radiation. Further, nodules are considered a sensitive sentinel for evidence of low-dose radiation effects (*9*), and their presence has been linked with the subsequent development of thyroid cancer (*10–12*).

Thyroid nodularity has been reported to be excessive among long-term residents of an area neighboring on a uranium waste-disposal site in Pennsylvania (*13,14*). Gamma radiation levels of 15–40 μR/hour (130–350 mR/yr) were measured in contrast to a

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background rate of 8 μR/hour (70 mR/yr) in the surrounding geographic area. Physical examinations of 201 women from the exposed area revealed a marginally significant doubling of thyroid nodular disease (7.6% vs. 3.3%), defined as nodules, adenomas, or cancer. The authors suggested that studies of thyroid nodularity, rather than cancer per se, might further illuminate the potential effects of low radiation doses.

Since 1972, the High Background Radiation Research Group (HBRRG) has studied the health of the population of two neighboring regions in the People's Republic of China with markedly different background levels of ionizing radiation (*15,16*). About 75,000 people from each region have been under study. In comparison with the high background radiation areas of India and Brazil (*17,18*), the Chinese area lends itself far better to epidemiologic study because of population homogeneity and stability. The people are farmers of mainly Han extraction whose families have been in the area for many generations. The present study was designed to test the hypothesis that a twofold difference in background radiation would produce a detectable increase in thyroid nodularity, and to learn whether chromosome aberrations in circulating blood lymphocytes would be noticeably increased.

Subjects and Methods

Radiation Exposure

In Yangjiang County, Guangdong Province, bordering on the South China Sea, there are two regions that cover about 540 km^2 where thorium-containing monazites have washed down from nearby heights and raised the level of background radiation to 2.9 times that of nearby areas similar in altitude and population (fig. 1). The average annual whole-body exposures from external radiation (primarily gamma rays) have been previously determined to be, on average, 330 mR in the high dose region and 114 mR in the nearby sections of Enping and Taishan Counties, which were selected as control areas by the HBRRG (*16*). These are areas of similarly high population density, and their exposure distributions do not overlap. Based on a transmission factor (cf., *19*) of 0.75 (Kaul D: personal communication), i.e., the factor to convert external exposure from thorium gamma rays in mR to thyroid gland dose in cGy, cumulative thyroid doses are estimated to be approximately 12–16 cGy and 4–6 cGy for women aged 50–65 years in the two regions. The variation in annual whole-body doses ranges between 0.18 and 0.28 cGy within the high background regions and between 0.06 and 0.09 cGy within the control regions. Dietary investigations, measurements of body burdens, measurements of radioactive radon, thoron, and their daughter products both indoors and outdoors, and autopsy studies all suggest that internal exposures contribute minimally to the radiation dose to the thyroid.

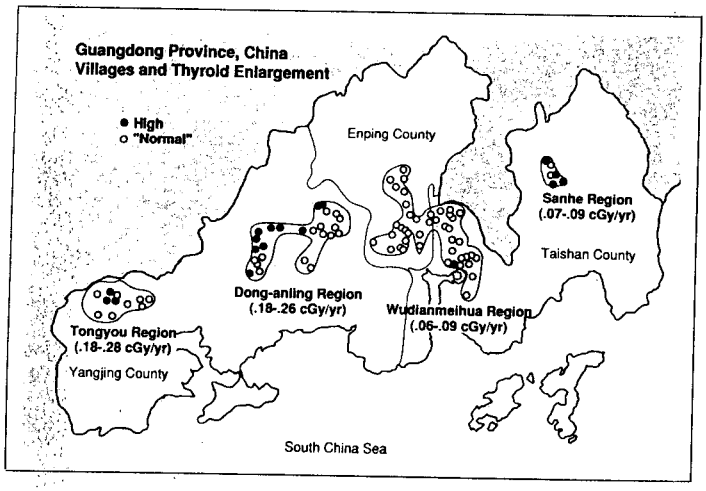

Figure 1. Distribution of most villages and thyroid enlargement among examined women who resided in areas of high and low background radiation in Guangdong Province, China. High background regions include Tongyou and Dong-anling, where the annual whole-body dose ranged between 0.18 and 0.28 cGy. Low background regions include Sanhe and Wudianmeihua where annual doses ranged between 0.06 and 0.09 cGy. Each village is represented by an open circle (○) within the four regions. Villages with prevalence rates in the upper 20% of the observed range were arbitrarily classified as villages with "high" prevalence of thyroid enlargements, and these villages are represented by a solid circle (●).

Survey Design

The survey was confined to older women who were born in the relevant counties and who had never been away from home for more than 3 months; therefore, cumulative thyroid doses would be maximal. Women over age 65 years were not included because it was felt they might be less able to tolerate the sometimes lengthy bus ride over relatively rough terrain to the examination centers. Many of the women had never before left their villages.

In March 1986, there were 6,710 women age 50 years or older in the high background area and 7,830 in the control area. Among them were 1,876 women aged 50–65 years living in the high background area and 2,806 in the control area. To detect a relative risk of 1.6 or higher, a study of 1,000 women in each exposure group had an 80% chance to show a difference in the prevalence of thyroid nodularity at the 0.05 level of significance. Representative samples of 1,100 each were chosen based on sampling ratios of 11 of 19 and 11 of 28 applied randomly within villages in the respective regions. Although the goal was 2,000 examined women, an extra 10% were chosen in the expectation that some women might not be available for examination.

With the approval of the Chinese Ministry of Public Health and Guangdong public health officials, meetings were held with village and hamlet leaders, the sampling frame was established, and the survey was explained to the 2,200 women who were chosen for study. In a 3-day pilot study in March 1986, 217 women from both areas were examined by one of the U.S. thyroidologists (M. M. Kaplan) with the assistance of Chinese physicians and both U.S. and Chinese support personnel. Chromosome preparations were made but thyroid blood tests were not performed. Because there were no major changes in the examination procedures between the pilot study and the full investigation, we present here the combined results regarding thyroid nodularity and chromosome abnormalities.

With the inclusion of the pilot subjects, 2,006 women, or 91% of the 2,200 selected, were examined. Informed consent was obtained from all participants. Table 1 gives the distribution of the survey sample by examination status and the reason some women were not examined. To minimize travel in November 1986, three examination centers were employed in succession. A mix of high background area and control subjects was brought to each center by bus to keep the examiners blind to subjects' exposure status. The examination centers (Enping, Taishan, and

Table 1. Characteristics of the sample of women residing in the high-background radiation and control areas in China

Characteristic	Background radiation		Total
	High	Control	
No. of women living in study areas			
≥50 yr of age	6,710	7,630	14,340
50–65 yr of age	1,876	2,806	4,682
No. selected for examination	1,100	1,100	2,200
No. examined	1,001	1,005	2,006
No. not examined	99	95	194
Reason for no examination			
Deceased	5	9	14
Sick*	20	26	46
Moved from area	18	38	56
Uncooperative	19	7	26
Not invited†	37	15	52

*Includes psychosis, deafness, blindness, and motion sickness.
†Part of the 10% reserve group not needed to fill the quota of 1,000 examinees in each group.

Yangjiang) were located in three of the four study regions (fig. 1), and the examiners had no knowledge as to whether a bus load of women came from a high background area or a control region.

Interview and Physical Examination

Before the physical examination, each woman was interviewed by a trained Chinese interviewer to provide information on relevant medications, medical and reproductive history, specific symptoms relevant to thyroid function, any thyroid surgery, family history of thyroid disease, smoking habits, diagnostic and therapeutic x-ray procedures, and diet history. The diet history placed emphasis on the iodine, salt, and goitrogen content of foods (*20–22*).

Physical examinations were conducted by three U.S. thyroidologists (M. M. Kaplan, H. R. Maxon III, and A. B. Schneider) blinded to the exposure status of the examinees. Any thyroid abnormality, or any uncertain abnormality, noted by one examiner was reviewed by another and by a third if necessary to reach consensus. A second examiner also evaluated a randomly selected 10% sample of all subjects, whether or not the first examiner found an abnormality. The results of the initial examiner were not revealed to subsequent examiners until after all findings were recorded. Each case was classified according to the final consensus of the examiners. Thyroid disease was classified as follows: single nodules, multiple nodules, enlargements, or other specific abnormalities. Eight cases in which consensus could not be reached were counted as possible (or uncertain) nodules. Nodules of 1.5 cm diameter or greater were referred to Chinese physicians for needle aspiration biopsy; specimens were to be read by pathologists at the Sun Yat-Sen University of Medical Sciences, Guangzhou. Subjects found to have clinically evident thyroid conditions were referred to local medical care facilities for follow-up. A local physician was also available to women who desired medical consultations for existing ailments.

Laboratory Measurements

Serum levels of thyrotropin (TSH), triiodothyronine (T3), thyroxine (T4), and anti-thyroid microsomal antibodies (AMA) were measured by radioimmunoassays in routine clinical use in the China Navy Radioimmunoassay Center, Beijing, where the study samples were assayed. Laboratory tests were performed on 10% of all subjects and on all subjects with thyroid abnormalities not in the 10% sample in the November 1986 survey. Unfortunately, the TSH mean values were below the practical limit of sensitivity of the assay used and thus judged to be uninformative. Urinary iodine and iodine–creatinine ratios were also measured in a random 4% sample of all subjects. Due to technical problems, determinations made on the initial serum samples were unsatisfactory, and repeat samples were obtained in November 1987 from 551 of the 600 women who had had blood drawn previously. During November 1987, additional urine samples were collected from 280 of these 551 women to determine urinary iodine and iodine–creatinine ratios on a larger sample of 14% rather than 4%. Iodine–creatinine measurements were the responsibility of the Laboratory of Industrial Hygiene (LIH) in Beijing.

The physical examinations revealed a high prevalence of thyroid abnormalities, which raised concern that deficiencies in dietary iodine might exist. Accordingly, salt samples were obtained from representative locations, usually local saltworks, in each county. Twenty samples were submitted to the Iodine Research Laboratory, Endocrinology Division, University of Massachusetts Medical Center, Worcester, MA for analysis of iodine content.

Cytogenetics

Venous whole blood was collected from 100 women from each of the two areas to determine the frequency of chromosomal aberrations in circulating lymphocytes. Cultures were established shortly after blood drawing by dispensing 1 mL of whole blood into 10 mL of complete medium (i.e., 9 mL of RPMI-1640, supplemented with 20% fetal bovine serum, 1% phytohemagglutinin, and 1% antibiotic solution). To arrest all responding lymphocytes at the metaphase stage of their first in vitro mitosis, colcemid (0.1–0.2 μg/mL) was added at the beginning of the culture period. Cultures were incubated at 37 °C for 48 hours and harvested by standard procedures. Metaphases were analyzed from coded preparations from each subject for all types of structural chromosome aberrations following detailed scoring procedures (*23*). Four Chinese cytogeneticists of the LIH staff, Beijing, each scored 25% of the slides. The slides from 50% of the preparations were subsequently reviewed at the Oak Ridge Associated Universities, TN.

Statistical Methods

The interview and physical examination forms were reviewed and transcribed onto coding sheets by the U.S. investigators in China and were then carried to the United States for analysis. The statistical analyses were made by standard methods for the comparison of the prevalence of single nodules or other thyroid abnormalities in the two regions. Unadjusted comparisons were based on chi-square tests for independence in contingency tables. For specific outcomes, the data were summarized in two-by-two tables and the significance tests were equivalent to the usual test for the equality of proportions. Prevalence ratios (RR) and confidence intervals (CI) were computed by standard methods (*24*). Demographic, dietary, and medical history data from the two regions were compared in several ways. For continuous and

ordinal variables such as age at first pregnancy or the diet frequency data, the sample means in the two regions were compared by means of *t*-tests. In addition, these variables were classified into *k* categories (five or less) based on their distributions in the whole sample; a test for independence in the resulting two-by-*k* contingency table was carried out. Unconditional logistic regression was used for multivariate analyses in which any area differences in the prevalence of single nodules or other thyroid abnormalities were adjusted for the effects of diet frequency, reproductive history, or laboratory test results.

Results

General Characteristics

The 1,001 women examined from the high-background area were compared with the 1,005 women from the control area as to demographic, reproductive and medical history, and diet. Although the two groups were generally very similar, a number of fairly small differences achieved statistical significance in samples of this size (table 2). Women from the high background area were younger at first pregnancy, had more children born alive, had fewer siblings, and lived in larger households in 1986. Fewer of them smoked tobacco, used various medicines, or had ever had chest fluoroscopy. On most other aspects of their medical histories, differences between the women of the two areas were not statistically significant at the .05 level. In particular, there was no evidence for differences in symptoms suggestive of thyroid disease or any personal or family histories of thyroid disease. Women in the high background area reported less frequent consumption of cassava and more frequent consumption of tofu, foods of high iodine content (i.e., seaweed and sea fish), and cruciferous vegetables. Salt consumption in the two areas appeared to be about the same in terms of both the frequency of eating salt-containing foods and their estimated salt content (grams/month). Chemical analysis of salt samples obtained from both regions revealed surprisingly low iodine content in both areas, less than 50 ng of iodine per gram of salt in all samples tested.

Table 2. Selected differences in the questionnaire responses of women residing in the high background radiation and control areas in China

Questionnaire information	Background radiation		*P* value
	High	Control	
No. interviewed	1,001	1,005	
Demographic and reproductive history			
Mean age at interview (yr)	58.09	58.25	.410
Mean age at first pregnancy (yr)	20.59	21.07	<.001
Mean No. of live births	6.52	6.23	.003
Mean No. of siblings	3.36	4.75	<.001
Mean No. in household	6.03	5.81	.030
Medical history			
Smokers (%)	0.6	2.7	<.001
Taking drugs for arthritis (%)	2.8	9.4	<.001
Taking drugs for chronic pain (%)	10.0	17.0	.001
Taking thyroid medicine (%)	0.9	2.1	.030
History of any chest fluoroscopy (%)	15.5	21.6	.001
Monthly frequency of specific dietary items			
Cassava	2.6	3.9	.020
Tofu	3.4	1.9	<.001
Foods of high iodine content	44.1	41.2	.040
Cruciferous vegetables	110.9	107.2	.060
Allium vegetables (garlic, chives, onions)	17.7	16.5	.380

Thyroid Abnormalities

Figure 2 gives a graphic description of the results of the physical examination, and table 3 provides counts of thyroid abnormalities by area. The high and low background areas did not differ in the prevalence of thyroid nodules, whether single or multiple (9.5% vs. 9.3%, $P > .5$), but did differ in the prevalence of thyroid enlargement or goiter (23.3% vs. 18.6%, $P < .001$). The increased prevalence of goiter among women in the high background area was due entirely to relatively small enlargements, less than two times normal gland size (table 4). The overall frequency of all abnormalities, 24.9% for women of the high background area and 21.3% for women of the control area, also differed significantly ($P = .05$). The distribution of nodule size as estimated by the examiners was similar among the women residing in both areas (table 5).

When the frequency of single nodules was examined by means of logistic regression for the effect of both area and the relevant dietary variables (cassava; cruciferous vegetables such as cabbage; tofu; allium vegetables such as garlic; foods of high iodine content; and salt consumption), influence was seen only for allium vegetables (garlic, chives, and onions). The prevalence of nodules in women who ate garlic, chives, and onions daily was 17% less than in women who ate no allium vegetables. None of the dietary variables was significantly associated with the fre-

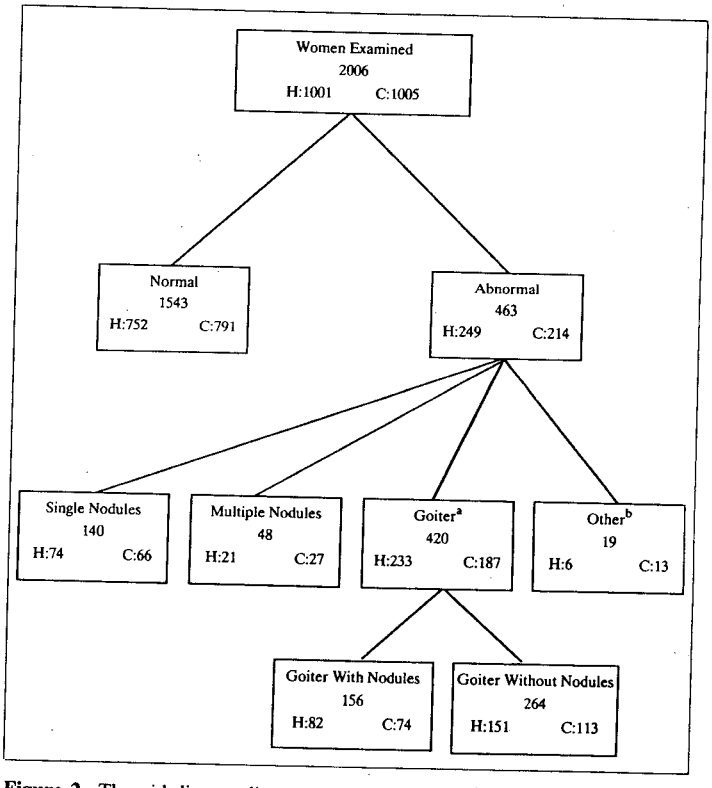

Figure 2. Thyroid disease diagnoses based on physical examination of 2,006 women. H: denotes high background radiation area; C: denotes control area. [a]Includes 156 women with nodules and five women with uncertain nodules. [b]Includes eight women with nodules or goiter and seven women with uncertain nodules.

Table 3. No. of thyroid abnormalities found on physical examination of women residing in high background radiation and control areas in China

Type of abnormality	Background radiation		RR	95% CI
	High (n = 1,001)	Control (n = 1,005)		
All nodular disease	95	93	1.02	0.76–1.35
Single nodule (any)	74	66	1.13	0.82–1.55
With goiter	61	48	1.28	0.88–1.84
Without goiter	13	18	0.73	0.36–1.48
Multiple nodules (any)	21	27	0.78	0.44–1.37
With goiter	21	26	0.81	0.46–1.43
Goiter (any)	233	187	1.25	1.05–1.48
With nodules	82	74	1.11	0.81–1.52
Without nodules	151	113	1.34	1.07–1.68
Other abnormalities (any)*	6	13	0.46	0.18–1.21
Without nodules or goiter	3	8	0.38	0.10–1.42
Any abnormality	249	214	1.17	1.00–1.37

*Women with uncertain nodules are included in these categories.

quency of thyroid enlargement or had any effect on the magnitude of the difference between the two areas in this respect. No significant associations were found in the analysis of thyroid nodularity or goiter in relation to reproductive history variables, age at first pregnancy, number of pregnancies, or number of live births.

Women residing in the high background radiation and control areas differed significantly with regard to smoking status, drug use, and exposure to chest fluoroscopy (table 2). None of these factors, however, was associated with increased thyroid nodularity. Although 15%–22% of all women had a history of exposure to chest fluoroscopy, few such examinations were performed; i.e., the mean number of fluoroscopies was 1.6.

To examine the geographic distribution of thyroid enlargement, villages were ranked by estimated prevalence. Villages with prevalence rates in the upper 20% of the observed range were arbitrarily classified as villages of high prevalence. Over half of the villages of high prevalence were located along the northern and western edges of the Dong-anling region of the high background radiation area (fig. 1). Estimated radiation exposure levels in these villages tend to be lower than the levels in other high background villages. There were also suggestions of small geographic clusters of villages of high prevalence in the Tongyou region of the high background area (three villages) and in the small Sanhe region in Taishan County of the control area. Only one of the high prevalence villages was located in the large Wudianmeihua region of the control area.

Table 4. Percentage distribution of thyroid gland size found on physical examination of women residing in high background radiation and control areas in China

Thyroid gland size	Background radiation	
	High (%) (n = 1,001)	Control (%) (n = 1,005)
Normal	76.7	81.4
Enlarged	23.3	18.6
Enlargement factor*		
1.1–1.9	15.3	9.8
2.0–2.9	5.4	5.6
3.0–4.0	1.9	2.0
>4.0	0.7	1.2

*Estimated enlargement times normal size.

Table 5. Percentage distribution of thyroid nodule size found on physical examination of women residing in high background radiation and control areas in China

Nodule size* (mm)	Background radiation	
	High (%) (n = 1,001)	Control (%) (n = 1,005)
None†	90.5	90.8
<10	2.0	2.0
10	2.5	1.4
11–14	2.0	1.7
≥15	3.0	4.1

*For multinodular glands, the estimated size of the largest nodule was used in these distributions.
†Includes uncertain nodules.

Laboratory Findings

Table 6 shows the results of the laboratory tests by region. Significant differences between the high background radiation area and the control area were observed for the urinary iodine–creatinine ratio and the urinary–iodine concentration. Women in the high background area had higher iodine–creatinine ratios, but they had lower iodine concentrations than women in the control area. Sixty-five needle biopsies were attempted but, for technical reasons, the resulting preparations proved difficult to evaluate and no results can be reported. Although there were no differences in the level of AMA between women in both exposure groups, women with thyroid enlargement had significantly higher levels of AMA than women without thyroid enlargement. The clinical findings of thyroid disease in rural Guangdong Province, including the laboratory measures, will be the focus of a separate report.

Table 6. Average laboratory values from serum and urine tests of women residing in high background radiation and control areas in China

Test	Background radiation		P value
	High	Control	
Serum T4 (μg/dL)	7.65 ± 0.10	7.70 ± 0.14	.770
Serum T3 (ng/mL)	1.05 ± 0.02	1.04 ± 0.03	.750
Serum TSH (μU/mL)	*	*	—
Serum AMA (% binding)	8.63 ± 0.50	8.36 ± 0.40	.670
Urinary iodine–creatinine ratio (μg/g)	132.20 ± 5.96	93.85 ± 5.25	<.001
Urinary iodine (μg/dL)	6.62 ± 0.24	8.10 ± 0.72	<.001
	No. of subjects tested		
Thyroid assays	289	261	
Urinary iodine	152	127	

*The mesaured values of TSH were not interpretable. The range of values for TSH in both normal and hyperthyroid patients using this assay was 0–9 μU/mL. Only three values were greater than this limit, and none was greater than 10 μU/mL.

Cytogenetic Findings

Chromosome aberration frequencies in circulating lymphocytes were determined for 200 women residing in the high background radiation and control areas. Twenty thousand cells were examined—100 cells per woman. Overall, and for each category of stable aberrations (translocations, inversions, and chromosomes with deleted segments) and unstable aberrations (dicentrics and rings), women in the high background area had increased numbers of detectable abnormalities (table 7). Results of an independent review of nearly 50% of the cytogenetic material (>9,000 metaphases) were in concordance with the original scoring of chromosome aberrations: the proportions of metaphases with stable aberrations compared to original values were 0.28 vs. 0.29 and 0.16 vs. 0.18 for high background areas and control areas, respectively. For unstable aberrations, the comparisons were 0.11 vs. 0.16 for high background areas and 0.07 vs. 0.06 for control areas.

Discussion

The nuclear reactor accident that occurred in 1986 in Chernobyl, USSR, and the ensuing worldwide dispersion of radioactive materials, particularly radioactive iodine (^{131}I), which lodges in the thyroid gland, have prompted further concern about the potential hazards of low doses of radiation delivered over relatively long periods of time (*25–27*). Estimates of cancer risk that might result from such exposures, however, are based in large part on studies of populations exposed to relatively high doses over short periods of time and do not take into account the possibility that radiation damage might be repaired when exposures are spread over many years (*28,29*). Excess thyroid cancers, for example, have not been seen in studies of persons exposed to relatively high doses (50 cGy) of diagnostic ^{131}I where the 8-day half-life is associated with a relatively low dose rate (*30*). The high background radiation area of south China provided one of the few opportunities in the world to study directly the effects of low doses of external radiation experienced over a lifetime.

The survey was designed on the assumption that a twofold risk of nodular thyroid disease, including cancer, might be found in the women in the high background area, compared to the women in the control area, if the survey results of Radford et al. (*13*) and Talbott et al. (*14*) were confirmed. However, the observed percentages of 7.4 and 6.6 for single nodules (RR = 1.13; 95% CI = 0.8–1.6) provide little support for this hypothesis, and a doubling of risk after a lifetime exposure difference of approximately 9 cGy to the thyroid from external gamma radiation can be rejected with high assurance.

Thyroid cancer has occurred excessively following childhood exposures of 9 cGy to external x rays delivered at a high dose rate (*7*). In contrast, the protracted nature of the exposures in China over so many years may have resulted in a great deal of cellular repair. Further, the influence of age might be important since the risk of radiogenic thyroid cancer appears to decrease with increasing age at exposure (*5,7*). If this is true, then women in the high background areas would have received much of their exposure to radiation during ages of relatively low sensitivity for tumor induction.

Although thyroid cancer was not evaluated per se, thyroid nodules have been found to be associated with the subsequent development of thyroid cancer in several recent studies (*10–12*), and biopsy specimens of thyroid nodules in irradiated thyroid glands often reveal a high proportion of malignancies (*1,3,9,31*). Assuming that the risk factors for nodules might be similar to those for cancer, we evaluated whether factors previously related to thyroid cancer risk, such as multiparity, consumption of shellfish, and decreased consumption of cruciferous vegetables (*12*), occurred disproportionately among women from either the high background or control areas. Although some differences were observed, none was substantial, and controlling for them in a multivariate analysis did not modify the study results to any extent. Increased consumption of vegetables of the allium class was linked to a significant 17% decreased prevalence of thyroid nodules. This observation is noteworthy since intake of garlic and onions was found to lower the risk of stomach cancer in China (*32*). Also, experimental studies show that onion and garlic oil can inhibit tumor growth and proliferation in laboratory animals (*33*). Consumption of cassava, a dietary goitrogen, was higher among the control women but was not independently related to nodular disease.

Iodine was absent in the salt used by women in both regions, consistent with previous reports (*20*). A lack of dietary iodine might partially explain the high prevalence of thyroid enlargement (18%–23%) observed in both survey regions compared to populations of elderly women who were similarly examined in the United States (4%) (*34*). Women residing in the high background area had a higher prevalence of minimally enlarged thyroid glands than did the control women, but the reasons for this increase are not entirely clear. Meaningful differences in dietary factors, including various measures of iodine and goitrogen consumption, were not apparent on the basis of the interview data. Urinary iodine–creatinine ratios were higher among women from the high background area, but urinary iodine concentrations were significantly lower than those of the controls. Because of significant variations in creatinine excretion due to malnutrition

Table 7. Summary of cytogenetic findings among women residing in high background radiation and control areas in China

Characteristic	Background radiation		*P* value
	High	Control	
No. of subjects	100	100	
No. of metaphases scored	10,000	10,000	
Proportion of metaphases* (± SE) with			
Stable aberrations†	0.29 (0.06)	0.18 (0.04)	.14
Translocations	0.14 (0.03)	0.12 (0.04)	.69
Inversions	0.07 (0.03)	0.05 (0.02)	.55
Deletions	0.09 (0.04)	0.02 (0.01)	.10
Unstable aberrations‡	0.16 (0.04)	0.06 (0.02)	.04
Total, stable + unstable aberrations	0.44 (0.07)	0.23 (0.05)	.02

*Mean No. of metaphases with aberrations per 100 metaphases per individual, standard error in parentheses; 100 metaphases from 100 women from each area were analyzed.

†Translocations, inversions, and chromosomes with deleted segments.

‡Dicentrics and rings. Fragments not included due to the difficulty in distinguishing isobreaks from fragments. Practically all the unstable aberrations were dicentrics.

in endemic goiter areas, some investigators have suggested that the iodine–creatinine ratio from casual urine samples in a community is not a good indicator of iodine deficiency, and thus recommend measuring the iodine concentration directly (*35*). Conceivably, the increased prevalence of mild goiter in the high background area might be due to dietary deficiencies of iodine, or to other environmental factors that we were not able to identify.

Only small increases in gland size (1.1–1.9 times normal) were found to be excessive among women in the high background area, and there were no differences for larger goiters. Since radiation has not been convincingly linked to simple nontoxic goiter (*12,31*), the significance of these observations remains unclear. Many of the villages where women with increased rates of goiter lived appeared to cluster along the foothills of a mountain range at some distance from the South China Sea (fig. 1). This suggestion of a nonuniform geographic distribution of goiter within the high background and control areas implies that factors other than radiation may be associated with the patterns of goiter and possibly other thyroid disease.

Radiation-induced chromosome aberrations in cultured lymphocytes have been reported in numerous studies of exposed persons, including atomic bomb survivors (*36,37*), nuclear shipyard workers (*38*), and patients irradiated for ankylosing spondylitis (*39*) and for cervical cancer (*40*). In our study, a significant elevation in the combination of stable and unstable chromosome abnormalities was detected among the residents of high background radiation areas. The increases for both aberration types were in the direction and magnitude expected if continuous exposures to radiation were responsible. Although stable and unstable aberrations are induced by radiation at the same rate, unstable aberrations decrease more rapidly over time. Thus, as anticipated, more stable aberrations were observed. Interestingly, the overall frequency of aberrations among the Chinese women was much lower than that found among the controls, or minimally exposed subjects, in other series of irradiated populations who used similarly stringent scoring procedures (*23,37,40*). This finding suggests that the women in rural China are not exposed excessively to such factors as diagnostic x rays or mutagenic chemicals that could increase chromosome aberrations. Conceivably, this low background rate for chromosome abnormalities enhanced our ability to detect a radiation effect.

Several methodologic issues should be kept in mind for the interpretation of our findings. The strengths of the study include: (*a*) the existence of well-defined populations of different exposure levels for which rosters could be prepared and large numbers could be sampled for clinical examination; (*b*) the blinded nature of the physical examination by expert thyroidologists; (*c*) the quality control measures for ensuring uniformity in the physical examination; (*d*) the extensive research already conducted on natural background radiation and its association with human disease in these populations (*15,16,41*); (*e*) the extensive dosimetry previously conducted that permits relatively accurate lifetime estimates of thyroid dose (14 vs. 5 cGy); (*f*) the stability of the populations in the high background radiation and control regions that facilitates the estimation of lifetime radiation exposures; (*g*) the low prevalence of cigarette smokers, medical x-ray exposures, previous thyroid surgeries, and hormone use that minimized the influence of possible confounding factors; (*h*) the ability to examine large numbers of women centrally and in a very short period of time; and (*i*) the extremely high (97%) participation rate.

Limitations of our study include the possibility that the women in the areas differ significantly with regard to unknown environmental and dietary factors associated with thyroid nodularity and cancer. Although such factors have been postulated (*42*), and cultural and educational levels appear to be higher in the control regions (*41*), no major dissimilarities in known risk factors for thyroid cancer were identified that could account for our negative findings with respect to nodules. Nonetheless, the apparent clustering of goiters within both study areas and the significant difference in urinary iodine concentrations indicate that factors other than radiation levels exist that we were not able to evaluate and which conceivably could have hindered our ability to detect a small radiation effect. The high prevalence of goiter in both regions also could have obscured a real radiation effect if the increased size of the thyroid gland made the detection of small nodules difficult. It seems unlikely, however, that the mild enlargements observed, between 1.1 and 1.9 times normal, would have been sufficient to obscure a twofold difference in nodular disease.

It is well established that ionizing radiation causes thyroid cancers and nodules, and doses of the order of 9 cGy have been linked to significant increases in thyroid nodules and cancer following acute exposure in childhood (*7*). Although it is practically impossible to rule out completely very small radiation effects, our study results are different from what would be predicted from studies of somewhat higher doses and much higher dose rates. We conclude that an excess thyroidal exposure of about 9 cGy delivered over a lifetime is not associated with an increased risk of clinically detectable thyroid cancer.

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