

## EXTERNAL RADIATION AND THE THYROID CANCER RISK IN HUMANS

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Numerous epidemiologic studies have clearly demonstrated that acute, external radiation exposure increases the frequency of thyroid neoplasia in humans, particularly when the exposure occurs during early childhood. Studies of the survivors of the atomic bombings in Hiroshima and Nagasaki, as well as of populations receiving radiotherapy for benign or malignant diseases have been the major sources of information about radiation-induced thyroid cancer. Although the studies were conducted in several countries using different methodologies, the risk estimates for childhood exposure are fairly consistent and a linear dose-response relationship describe the data well. In contrast, adult exposure to external radiation has not been linked to thyroid cancers.

The clinical course of radiation-associated thyroid cancers depends on whether they are detected during routine care or during early-detection screening. Thyroid cancer incidence increases markedly when irradiated populations are screened; however, the slope of the dose-response relationship does not appear to change significantly. With screening, the fraction of patients diagnosed with cancers <15 mm is significantly higher than when thyroid cancers are diagnosed during routine medical care.

### 1 INTRODUCTION

The thyroid gland in children is particularly vulnerable to the tumorigenic effects of ionizing radiation (1-3). A linear dose-response relationship has been demonstrated in most studies of persons exposed to x- or gamma radiation during childhood or adolescence, and the excess risk appears to persist for decades. Less is known about adult exposure, but current data indicate that the adult thyroid gland is relatively insensitive to the tumorigenic effects of radiation. During the last ten years, several new or updated studies on radiation and thyroid cancer have been published. The data from these studies suggested that a pooled analysis could help answer some of the remaining important questions concerning the shape of the dose-response relationship, the effect of gender and age at exposure, the pattern of risk by attained age and time since exposure, and the influence of fractionated exposure on risk.

## 2 EVIDENCE OF AN ASSOCIATION BETWEEN RADIATION AND THYROID CANCER

The major single source of data on thyroid cancer and external radiation is the Life Span Study (LSS) of the atomic bomb survivors in Hiroshima and Nagasaki, Japan (4), but knowledge about radiation-associated thyroid tumors also comes from a variety of studies of medical (diagnostic, radiotherapy for benign and malignant disease), occupational (medical workers, nuclear workers) and environmental (persons exposed to fallout from bomb testing, naturally high background areas) areas (1). Until the 1960s, radiotherapy was used frequently to treat a wide variety of benign diseases. Studies of these medically irradiated populations have provided a great deal of information, but most concern childhood exposure. Studies of environmental and occupational exposures have been much less informative, partly because the doses are very low and, therefore, huge numbers of subjects are needed for adequate statistical power. In addition, occupational studies frequently are based on mortality data, which are not very useful for a relatively non-lethal disease such as thyroid cancer.

A pooled analysis of seven major studies of acute, external radiation exposure (with individual doses to the thyroid gland) was performed (5). The studies were conducted in several countries. Combined they included almost 120,000 people (about half were exposed), nearly 700 thyroid cancers and 3,000,000 person years of follow-up (4, 6-11). More women than men were in the total study population. Exposed children (less than 15 years old) were included in all but the study of cervical cancer patients, whereas data on adult exposures were available only from the studies of atomic bomb survivors and cervical cancer patients.

The data from each of the individual studies were consistent with a linear dose-response relationship, although there was a suggestion from the study of childhood cancer that the excess relative risk may level off at very high doses ( $>10$  Gy). The pooled  $ERR_{1Gy}$  was 7.7 (95% CI = 2.1, 28.7) and the  $EAR/10^4$  PYGy was 4.4 (95% CI = 1.9, 10.1) (Table 1). Risk estimates for three cohorts that are not included in the pooled analysis are consistent with those observed in the pooled analysis (12-14). In the pooled analysis, the excess relative risk decreased with increasing age at exposure; persons exposed between the ages of 10-14 years had one-fifth the risk of those exposed before age five years. The pooled analysis indicated that for persons whose thyroid gland was exposed to 1 Gy before age 15 years of age, about 88% of the cancers could be attributed to radiation exposure. The excess relative risk was highest 15-19 years after exposure, but remained elevated even after 40 years. Although the  $ERR$  per Gy was about two times higher for women than for men, this difference was neither statistically significant nor consistent across studies. There was weak evidence that fractionated exposure might have been somewhat less carcinogenic than acute exposure.

**Table 1.** Excess relative risk per Gy (ERR/Gy) and excess absolute risk per  $10^4$ PY-Gy (EAR/ $10^4$ PY-Gy)

	Excess relative risk model		Excess absolute risk model	
	ERR/Gy (95% CI)	P-value for linearity	EAR/ $10^4$ PY-Gy (95% CI)	P-value for linearity
<b>Exposure &lt;15 years old</b>				
Thymus	9.1 (3.6,28.8)	0.41	2.6 (1.7,3.6)	0.67
A-bomb (<15 ATB)	4.7 (1.7,10.9)	0.41	2.7 (1.2,4.6)	0.98
Tinea capitis	32.5 (14.0,57.1)	0.45	7.6 (2.7,13.0)	0.77
Tonsils (MRH)	2.5 (0.6,26.0)	0.24	3.0 <sup>a</sup> (0.5,17.1)	0.02
Childhood cancer <sup>b</sup>	1.1 (0.4,29.4)	0.09		
<b>Exposure 15 years old</b>				
Cervical cancer <sup>c</sup>	34.9 (-2.2, )	0.81		
A-bomb ( 15 ATB)	0.4 (-0.1,1.2)	0.38	0.4 (-0.1,1.4)	0.70

<sup>a</sup> This is the average excess absolute risk, however, the EAR/ $10^4$ PY-Gy was 2.4 (95% CI = undetermined,10.4) for follow-up until 1974 and 45.2 (95% CI = -3.2,89.0) for followup after 1974. The EAR/ $10^4$ PY-Gy estimates in this study are subject to large variability because of the influence of extreme dose points. These points, however, appeared to have little influence on the ERR/Gy.

<sup>b</sup> ERR/Gy estimates based on setting doses under 2 Gy to the mean dose of 0.74 Gy.

<sup>c</sup> ERR/Gy estimates based on regression of category-specific mean doses. It can be seen that the point estimate is not significant and the confidence interval is extremely large.

The broad range of ages at the time of the bombings makes the LSS the only study that allows a complete assessment of age at exposure effects. The risk of thyroid cancer decreased rapidly with age at the time of the bombings ( $p < 0.001$ ) (4). The excess relative risk for individuals under age 10 at exposure was significantly elevated ( $ERR_{1SV}=9.5$ , 95% CI= 0.11-18) and was over three times higher than for those who were 10-19 ATB. Among individuals over 20 years at exposure, there was no significant excess of thyroid cancer ( $ERR_{1SV}=0.10$ ; 95% CI=< 0.23, 0.75). A similar pattern was observed when an absolute risk model was used.

Microcarcinomas (i.e. small papillary carcinomas which are not clinically evident) are quite common at autopsy. The relationship between radiation exposure and these tumors has been studied in a series of autopsies among atomic bomb survivors (15). The risk of microcarcinomas increased with increasing dose among persons exposed to the bombings. The elevated risk continued for at least 40 years after exposure.

Since diagnostic x-rays are the largest man-made source of exposure to ionizing radiation for the general public, evaluating the role of fractionated exposure is particularly relevant for public health. An association between diagnostic x-rays and thyroid cancer has been reported in two case-control studies from Sweden (16,17), but results from case-control studies can be complicated by the problem of recall bias. To prevent this potential bias, a study conducted in Sweden was designed to obtain information on diagnostic radiation exposure by linking radiology records of diagnostic x-rays to thyroid cancer cases and controls identified through the Swedish cancer or population registries (18). Among 484 cases and an equal number of controls, there was no difference in the number of recorded medical x-rays. Furthermore, when estimated doses were calculated for each diagnostic procedure, no dose-response relationship was observed.

Early studies of radiation workers provided no evidence for an elevated risk of thyroid cancer. More recently, there have been a few positive reports. Since adult, acute exposures have not been linked to thyroid cancer, negative findings following protracted exposure are not surprising, however, the limitations of these occupational studies should be noted: individual doses were available only in the nuclear worker studies; multiple comparisons were made so probability of an increased risk occurring by chance is rather large; the number of thyroid cancer cases in each individual study was small resulting in unstable risk estimates; several of the investigations were based on mortality data and, thus, are not very informative for a disease with an overall 5-year survival rate of over 95%; and finally ascertainment may be better in a medically insured worker population than in the general public.

While most studies of fractionated exposure do not demonstrate in raised risks of thyroid cancer, it should be noted that many of the diagnostic x-ray and occupational exposures occurred among adults. Given the large difference in the sensitivity of the child and adult thyroid gland, it is not clear how fractionated or protracted radiation would affect young children.

### 3 CLINICAL COURSE OF RADIATION-ASSOCIATED THYROID CANCERS

The clinical course of radiation-associated thyroid cancers depends on whether they are detected during routine care or during early-detection screening. Routine screening has a very large effect on the estimated incidence of thyroid

nodules and thyroid cancer in exposed populations. The magnitude of the effect depends on how screening is performed. For the thyroid, the least sensitive method of screening is by palpation. A study from Boston compared questionnaire data with palpation findings for subjects irradiated during childhood and non-irradiated comparison subjects (11).

Clinically, the value of screening by palpation is limited. With the development of improved methods to image the thyroid, the large false negative rate of palpation, even for nodules 1.0 cm which are generally considered to be "clinically significant", has become apparent (19,20). More recently, the substantial rate of false positive findings (i.e., apparently palpable nodules that are not confirmed by thyroid ultrasound) has been emphasized (21).

Screening the thyroid with high sensitivity imaging, by isotopic scanning or ultrasonography, increases the observed rate of thyroid tumors even further. The magnitude of the increase depends on the size of the nodule used to define a positive endpoint. In the Michael Reese cohort of patients irradiated for enlarged tonsils, screening, predominantly with thyroid scans, began in 1974. By comparing incidence rates before and after 1974, it was found that the incidence of thyroid cancer increased by about 10-fold as a result of screening. However, the increase in detected tumors did not affect the ERR because it did not vary by dose (22). Thyroid ultrasound was studied in 54 representative subjects from the same cohort. Only seven subjects did not have nodules detected. Among the 47 screenees with nodules, 154 nodules were found, i.e. an average of 3.3 nodules per person (20).

Detection of radiation-related thyroid cancers during screening has a major impact on their clinical characteristics. This is illustrated by comparing the thyroid cancers diagnosed before and after the initiation of screening in the Chicago study (Table 2). The average size of the thyroid cancers discovered by screening was about half that of the cancers found during routine care. Before 1974, more cancers were diagnosed with lymph node metastases, but this is likely due to the younger age at discovery. The remainder of the clinical characteristics did not differ significantly.

The clinical behavior of the radiation-related thyroid cancers in the Chicago study was studied by correlating the presenting clinical features with the frequency of recurrence (6). In this cohort, it was concluded that radiation-related thyroid cancer is not unusually aggressive. In contrast, the recent findings from the Chernobyl-related thyroid cancer cases indicate that they may be more aggressive than expected. The Chernobyl results are largely based on the presenting histological characteristics of the thyroid cancers compared with thyroid cancers in non-irradiated children (24).

**Table 2.** Clinical characteristics of thyroid cancers detected during routine care compared with those detected during screening.

Characteristic:	Year of surgery for thyroid cancer	
	< 1974 (N = 126 <sup>a</sup> )	1974 (N = 262 <sup>a</sup> )
Average size (cm.)	1.89	0.95
Size 1.5 cm	52.3%	16.3%
Lymph node positive	54.3%	23.4%
Multicentric	62.2%	53.3%
Bilobar	30.6%	28.6%
Minor/major invasion	33.6%	24.8%
Major invasion	12.1%	9.6%

<sup>a</sup> Clinical characteristics are unknown for some cancers, so the number of cancers included in each category is not always equal to the total number of cancers.

Despite the wealth of existing knowledge about radiation-associated thyroid cancer, many issues remain unresolved because of insufficient data in individual studies. Future research on radiation-related thyroid cancer should be directed at quantifying lifetime risks, evaluating the long-term clinical course, ascertaining whether there are particularly susceptible individuals or groups that can be identified, and learning more about the carcinogenic effects of <sup>131</sup>I exposure, especially during childhood.

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