

# Familial Concordance of Thyroid and Other Head and Neck Tumors in an Irradiated Cohort: Analysis of Contributing Factors

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Relatively little is known about variations in susceptibility to the effects of radiation in the general population. We have been studying 4296 individuals exposed as children to head and neck radiation. The present study was designed to evaluate the pattern of thyroid, parathyroid, salivary, and neural tumors in irradiated siblings for evidence of heritable susceptibility factors. We also wanted to determine whether the characteristics of thyroid cancers were influenced by familial factors. The following criteria were met by 251 sibling pairs: both irradiated, both with follow-up (average,  $44.3 \pm 9.4$  yr; range, 9.4–59.5 yr), and both with organ-dose estimates. For each sibling pair we derived a quantitative score, taking into account the length of follow-up and known risk factors, for

their concordance and used the sum of these scores to characterize the population. Whether we used thyroid cancer or all thyroid nodules as an end point, the degree of concordance did not exceed what could be explained by the length of follow-up and known risk factors. For thyroid cancer, neither the presenting characteristics nor their rates of recurrence were influenced by their concordance status. In summary, we were unable to identify familial factors that modify the strong effects of radiation exposure. There is no reason to alter the evaluation or treatment of thyroid cancer in an irradiated patient based on whether another member of the family has radiation-related tumors. (*J Clin Endocrinol Metab* 89: 2185–2191, 2004)

IT HAS BEEN well established that external radiation to the head and neck area during childhood increases the risk of developing benign and malignant thyroid neoplasms (1–3). Hyperparathyroidism, salivary gland neoplasms, and neural tumors of the head and neck area have also been associated with childhood external radiation exposure (4–9). We have found a significant dose-response relationship and/or an excess number of cases of each of these neoplasms in a group of 4296 individuals who were exposed to external radiation before their 16th birthday whom we have been following since 1973. In this group, radiotherapy was used to treat various benign head and neck disorders, mostly enlarged adenoids and tonsils.

The study of this cohort has allowed us to look for patterns of tumors that would suggest that there is variable susceptibility to radiation in the general population. It is reasonable to expect such variation because some rare hereditary diseases, such as ataxia telangiectasia, are associated with a striking increase in susceptibility to radiation (10). However, it is less clear whether heterozygous carriers of these diseases or polymorphisms in other genes, such as DNA repair genes, are associated with radiation susceptibility (11–13). We hypothesized that if there were such susceptibility, an individual who developed one radiation-associated neoplasm might have an increased risk of developing a second. In a recent analysis of our cohort we did not find this (14).

Here, we analyze the occurrence of head and neck tumors

in irradiated sibling pairs to look for evidence of familial susceptibility. For the 251 informative sibling pairs in the cohort, we determined whether the distribution of tumors was random (*i.e.* based only on known risk factors, *e.g.* dose of radiation) or whether familial factors are involved.

Fifteen years ago, we carried out a more limited analysis (15). We revisited this question now because we have substantially improved the quality and quantity of the data as well as the statistical analysis. Many more thyroid and other head or neck neoplasms have developed during the 15 yr of follow-up, individual organ doses have been estimated (1), and there is a better understanding of risk factors for parathyroid, salivary, and neural tumors, including dose-response relationships for parathyroid and salivary neoplasms. We also devised new methods to include a wider range of neoplasms in the analysis.

As we observed an apparent excess of tumor concordance (presence or absence of neoplasms) in sibling pairs, we tested the hypothesis that after taking known risk factors into account, this excess was not a result of chance alone. We also examined thyroid cancers to determine whether their characteristics and behavior in one sibling were related to the presence of a radiation-related neoplasm (concordance) in the other sibling.

## Subjects and Methods

### Population at risk

Of 5373 patients who received external radiation treatment at Michael Reese Hospital between 1939 and the early 1960s for benign conditions of the head and neck area, 4296 were treated with conventional external radiation before their 16th birthday (1). These 4296 patients comprise the

study cohort. Radiation doses to specific organs were estimated for 3842 patients in the cohort (1). Follow-up was continued through December 31, 2000.

### Sibling groups

There were 677 subjects in sibling groups (two or more individuals) in the cohort of 4296 patients. Sixty-four individuals (32 pairs) were excluded because of the absence of follow-up information for one or both members of the sibling group. Of the 613 remaining subjects, 88 individuals (44 pairs) were removed for lack of thyroid-specific doses in one or both siblings. Among the remaining 525 individuals there were several sibling groups of three or four individuals. In these cases the elder two siblings were included in study. As a result, from three family groups with four members, six individuals were removed, and for 17 family groups with three members, 17 individuals were removed. This resulted in 502 individuals in 251 sibling pairs for the present study (Fig. 1). The mean ( $\pm$ SD) follow-up for these 502 individuals was  $44.3 \pm 9.4$  yr (range, 13.7–59.5).

### Follow-up, dosimetry, and definition of neoplasm end points

Information for this family study was obtained from the general surveys conducted for the entire cohort. Self-administered questionnaires were sent by mail. Included with the surveys was information about the potential risks of childhood radiation exposure. When a neoplasm was reported to us, based on surgery or other diagnostic findings, we obtained and reviewed the relevant medical records and specimens.

In analyzing thyroid cancer, years at risk was the time from initial radiation treatment to the date of first diagnosis for cancer (for those who developed cancer) or to the end of last known follow-up (for those who did not). The same model was used for neural (meningiomas, acoustic neuromas, and other Schwann cell tumors of the head and neck area) and salivary gland (benign and malignant) tumors.

Hyperparathyroidism was defined as elevated calcium levels with

elevated PTH levels and/or surgical correction of hypercalcemia by removal of one or more parathyroid glands. For those with hyperparathyroidism, years at risk were calculated from exposure until the date of surgery or, for those who did not have surgery, the date when the diagnosis was confirmed by an inappropriately high PTH level.

All 83 observed thyroid cancers, regardless of size, were included in the analysis. For seven of them, the size was not known, 32 were less than 10 mm (including 11 considered microscopic), and the remaining 44 (53%) were 10 mm or more. For some analyses, benign and malignant thyroid neoplasms were considered as a single end point. Previously, we showed that approximately 90% of the members of this cohort have ultrasound-detected thyroid nodules (16). Therefore, we limited this end point to neoplasms that were 10 mm or more in largest dimension determined at the time of surgery, by ultrasound, or by other diagnostic means. For this end point years at risk was defined as the interval between the date of initial radiation treatment and the date of surgery for nodules or, for those who did not have surgery, the date of diagnosis. The group consisted of 180 individuals with thyroid neoplasms (nodules) confirmed by surgical pathology to be malignant or benign and 10 mm or larger. Another 17 individuals with nodules were included based on the following findings: 14 had ultrasound documented nodules 10 mm or larger, and three had nodules 10 mm or larger by palpation.

Organ-specific radiation doses were estimated as reported previously (1). The dose for the thyroid gland was also used for the parathyroid glands. A weighted average of the doses to the different salivary glands was used as described previously (7). It is not possible to determine an average dose for the whole group of neural tumors given the wide range of tumor locations, so no dose estimates for these tumors are available.

### Risk factor analysis

For each individual, we needed to calculate the risk that they would develop each of the tumor end points (thyroid cancer, thyroid nodules, hyperparathyroidism, and salivary or neural tumors). We adapted statistical methods that were previously described in detail (14, 15). In brief, Cox proportional hazards analysis was used to define significant risk factors, taking years at risk into account (17). Each tumor end point was analyzed separately, and years at risk was specific to each end point. For example, individuals who developed thyroid cancer remained at risk for the other tumors until the end of their follow-up periods. For each risk factor (covariate) the regression coefficient and upper and lower confidence intervals were calculated, and a factor was considered significant if the range of the upper and lower 95% confidence intervals did not include 1.0. For both thyroid end points, dose, sex, and age at exposure were significant risk factors; for salivary tumors and hyperparathyroidism, dose was a significant risk factor, and no significant factors were found for the neural tumors. Risks are expressed as excess relative risk. Excess relative risk (ERR) and relative risk (RR) are related as follows:  $ERR = RR - 1$ .

The risk that an individual would develop each of the tumor end points was estimated as the cumulative hazard derived from the Cox analysis as follows. For each individual for each tumor, based on the number of years at risk, a basal hazard, with all covariates set at zero, was determined. Then the cumulative hazard was calculated, using the individual's actual set of risk factors. As a check, we confirmed that the sum of the cumulative hazards for all individuals for each tumor equaled the number of the tumors observed.

### Methods for defining familial factors

We are testing the hypothesis that familial effects influence the risk of development of radiation-induced head and neck neoplasms. If this were true, then the distribution of tumors within family pairs would not be accounted for by known risk factors. On the other hand, if familial factors do not influence the risk of development of these tumors, after taking into account years at risk, sex, age at exposure, and radiation dose, then the distribution of tumors would be independent of family pairs.

To test this hypothesis, for each individual we determined a residual for each tumor. The residual was defined as zero minus the cumulative hazard for subjects who did not develop the tumor and 1 minus the cumulative hazard for those who did. Each individual was then given a score equal to the sum of the residuals for the four tumors included in the analysis. Two sets of four end points were used: thyroid cancer

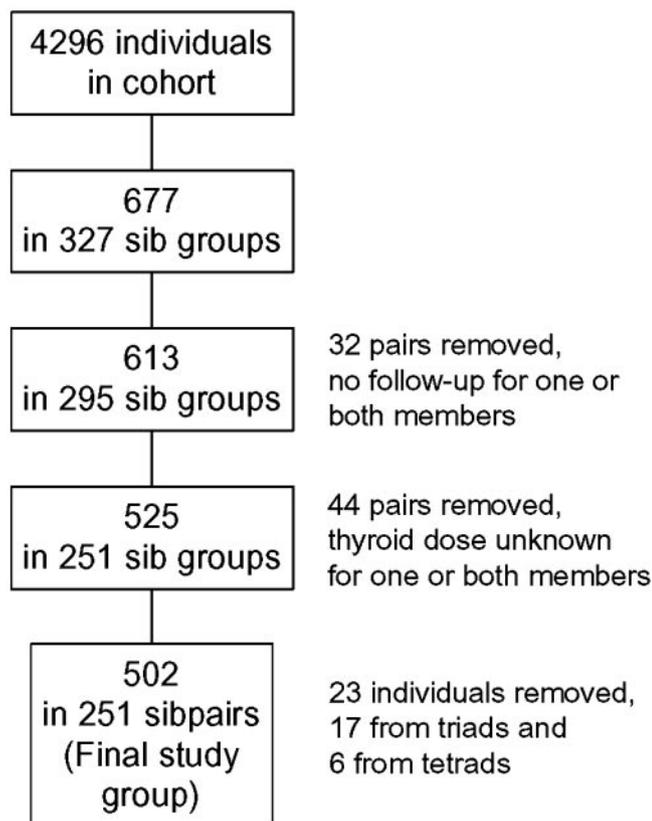


FIG. 1. Identification of the 251 sibling pairs who comprise the study population.

or thyroid nodules plus the other three tumors (parathyroid, salivary, and neural). The presence of neoplasms in both siblings or the absence of neoplasms in both indicated concordance. The more similar the residuals in the siblings (in either the positive or the negative direction), the stronger the concordance. Therefore, the product of the two residuals for each pair, referred to as the concordance score, was used as a quantitative measure of concordance. Concordant pairs have positive scores (the product of two positive or two negative numbers), and discordant pairs have negative scores.

The population of the 251 sibling pairs was characterized by the sum of the concordance scores. This sum has the property that when it is positive it indicates an excess of concordance, and the greater the number of concordant pairs, the higher it is. The sum of concordance scores was used to test the null hypothesis that concordance occurred randomly. To do this, the 502 individuals were used to randomly reconstruct 251 sibling pairs and to calculate the sum of concordance for the hypothetical population. This random pairing was performed  $10^3$  times, and  $10^3$  sums of concordance scores, with an average value of zero, were obtained. The null hypothesis could be rejected at level 0.05 if the sum of concordance scores for the actual sibling pairs was greater than 95% of the sums of concordance scores for the randomly generated permutations. Given the number of sibling pairs and the observed prevalence of neoplasms, and assuming that the Cox modeling removes effects due to sex, dose, and age at exposure, there is a greater than 80% power to detect an attributable risk of 4% (correlation coefficient:  $r = 0.2$ ;  $r^2 = 0.04$ ) using either thyroid cancer or thyroid nodules.

As a check on this methodology, familial effects were also assessed using interclass correlation of the residuals (18).

*Analysis of thyroid cancer behavior with respect to sibling concordance*

We used the following analytical methods to determine whether thyroid cancers in concordant sibling pairs differed from thyroid cancers among patients whose sibling had not developed a radiation-related tumor. The thyroid cancers were divided into two groups, defined by the status of the sibling, and were compared for presenting features by *t* test, for categorical variables by  $\chi^2$  analysis, and for recurrence by comparing the Kaplan-Meier plots using the log-rank and Breslow tests (SPSS, Inc., Chicago, IL).

**Results**

In the 502 individuals included in this study, there were 83 thyroid cancers, 197 thyroid neoplasms (benign and malignant), 15 cases of hyperparathyroidism, 14 salivary neoplasms, and 15 neural tumors.

*Analysis of the distribution of neoplasms in families*

Tables 1 and 2 show the distributions of neoplasms in the sibling pairs and the observed frequency of concordance. In Table 1, cancer is the thyroid-related end point, whereas in Table 2, nodules, including cancer, as defined in *Subjects and Methods*, is the thyroid-related end point. The other three end points (hyperparathyroidism, benign and malignant salivary neoplasms, and neural tumors) are the same in both tables. As a preliminary analysis of concordance, we compared observed *vs.* expected using simple binomial probabilities to determine the latter for all specific tumor combinations. The expected values shown in the tables, therefore, depend on the proportion of different tumors in the cohort, but not the presence of known risk factors or the length of follow-up. With thyroid cancer as the end point, the number of pairs concordant for no tumors and the pairs concordant for tumors were similar to those expected (152 *vs.* 146.36 and 13 *vs.* 13.91, respectively). With thyroid nodules, including cancer, as the end point, there was an apparent excess of sibling

**TABLE 1.** Observed and expected (uncorrected for years at risk and other risk factors) number of tumor combinations with cancer as the thyroid end point

Sibling 1		Sibling 2		Observed	Expected
No. of tumors	Type	No. of tumors	Type		
None		None		152	146.36
1		None		77	84.42
	ThyCa			54	
	Para			7	
	Sal			7	
	Neur			9	
2		None		8	6.03
	ThyCa, Para			4	
	ThyCa, Sal			2	
	ThyCa, Neur			2	
3		None		1	0.16
	ThyCa, Para, Neur			1	
1		1		8	12.17
	ThyCa		ThyCa	6	
	ThyCa		Neur	1	
	Para		Neur	1	
2		1		5	1.74
	ThyCa, Para		ThyCa	1	
	ThyCa, Sal		ThyCa	1	
	ThyCa, Sal		Sal	1	
	ThyCa, Neur		ThyCa	1	
	Sal, Para		Sal	1	

ThyCa, Thyroid cancer; Para, hyperparathyroidism; Sal, salivary gland tumor; Neur, neural tumor. For the purpose of showing all combinations, sibling 1 in this table is the one with the larger number of neoplasms. For each combination, the total expected is shown, but only the observed tumor patterns are listed. The additional combinations were not observed and account for 0.12 expected cases.

concordance for the absence of tumors (87 *vs.* 77.35). There was no apparent excess of concordance for both siblings having tumors (50 *vs.* 49.22), except when one or both had multiple tumors (11 *vs.* 7.19).

Figures 2 and 3 show the results of the analyses taking the length of follow-up and risk factors into account. In Fig. 2, cancer is the thyroid-related end point, whereas in Fig. 3, nodules, including cancer, is the thyroid-related end point. The *top panels* of these figures show the individual residuals, the difference between the observed and the expected number of tumors for each of the 502 individuals comprising the sibling pairs. The *middle panels* of these figures show the products of the sibling pair residuals, the measure of concordance in each of the 251 sibling groups. The *bottom panels* show the sum of products (the population concordance score) of actual sibling pairs in relation to the  $10^3$  concordance scores generated by random permutations and the fitted normal curve centered on zero, where zero is the distribution showing no concordance. The probability that the observed distribution is not due to chance (the level of significance) is shown by *shaded areas* under the curve. Using cancer as the thyroid-related end point, the null hypothesis could not be rejected ( $P = 0.32$ ). Similarly, using thyroid nodules, including cancer, although the *P* value was borderline, the null hypothesis could not be rejected ( $P = 0.075$ ).

We calculated the interclass correlation to determine the total variance of the residuals that is attributable to variation among families (Table 3). Familial variation accounts for only 2.4% of the total variance when thyroid cancer is one of the

**TABLE 2.** Observed and expected (uncorrected for years at risk and other risk factors) number of tumor combinations, using nodules as the thyroid end point

Sibling 1		Sibling 2		Observed	Expected
No. of tumors	Type	No. of tumors	Type		
None		None		87	77.35
1		None		101	114.19
	ThyNod			90	
	Para			2	
	Sal			4	
	Neur			5	
2		None		13	9.47
	ThyNod, Para			5	
	ThyNod, Sal			3	
	ThyNod, Neur			5	
1		1		39	42.03
	ThyNod		ThyNod	35	
	ThyNod		Neur	1	
	ThyNod		Sal	2	
	Para		ThyNod	1	
2		1		9	6.97
	ThyNod, Neur		ThyNod	2	
	ThyNod, Para		ThyNod	4	
	ThyNod, Sal		ThyNod	1	
	ThyNod, Sal		Sal	1	
	ThyNod, Para		Neur	1	
3		1		1	0.20
	ThyNod, Para, Neur		ThyNod	1	
3		2		1	0.02
	ThyNod, Para, Sal		ThyNod, Sal	1	

ThyNod, Thyroid nodule; Para, hyperparathyroidism; Sal, salivary gland tumor; Neur, neural tumor. For the purpose of showing all combinations, sibling 1 in this table is the one with the larger number of neoplasms. For each combination, the total expected is shown, but only the observed tumor patterns are listed. The additional combinations were not observed and account for 0.77 expected cases.

end points and for only 9.1% of the variance when thyroid nodules is used as one of the end points. The estimates of the significance of between-family significance agree very closely with the permutation method, as described above.

#### *Clinical behavior of thyroid cancer according to concordance in family*

To determine whether the presence of a radiation-related neoplasm in a sibling influenced the characteristics or clinical behavior of the 83 thyroid cancers included in this study, we made two comparisons. For each comparison, we divided the cancers into two groups depending on whether the sibling had a tumor (was concordant) or not. In the first comparison, a concordant sibling was considered one with thyroid cancer, hyperparathyroidism, a salivary tumor, or a neural tumor. In the second comparison, a concordant sibling was considered one with a thyroid nodule, including cancer, hyperparathyroidism, a salivary tumor, or a neural tumor. In the first comparison there were 20 concordant thyroid cancers and 63 discordant ones, whereas in the second comparison there were 38 concordant and 45 discordant thyroid cancers (Table 4).

We compared the characteristics of the thyroid cancers according to the status of the sibling, looking for features associated with more aggressive behavior in cancers in concordant sibling pairs (Table 4). However, there were no significant differences in latency, age at development, size, lymph node involvement, and multifocal or bilateral presentation of the cancers. Using Kaplan-Meier analysis, the disease-free survival times were compared for the thyroid

cancer groups (Fig. 4). Although the concordant cancers tended to show a higher rate of early recurrence, the differences were not significant and diminished with time.

#### **Discussion**

The primary goal of this study was to examine the pattern of radiation-related neoplasms in sibling groups for evidence of concordance above what could be explained by known risk factors. The methods that we developed for this analysis achieved four goals. First, they were able to account for time at risk and known risk factors. Second, they took into account multiple end points: in this case, thyroid tumors, hyperparathyroidism, salivary neoplasms, and neural tumors. Third, they were able to give individual weights to concordant and discordant pairs. For example, concordant pairs with multiple tumors had a greater weight than pairs in which each sibling had a single tumor. Fourth, they took into account concordance where both siblings had tumors and where neither sibling had a tumor. This is important because if there are genetic factors, they could, in principle, increase or decrease susceptibility to the effects of radiation.

Using these methods, we found that there was no excess concordance in sibling pairs; in other words, no evidence for familial risk factors. In addition to shared genetic factors, siblings would be exposed to common environmental factors during childhood and adolescence, as it is highly likely that they would have grown up in the same household. Thus, the findings do not support the existence of heritable or environmental factors that substantially alter radiation susceptibility in this group.

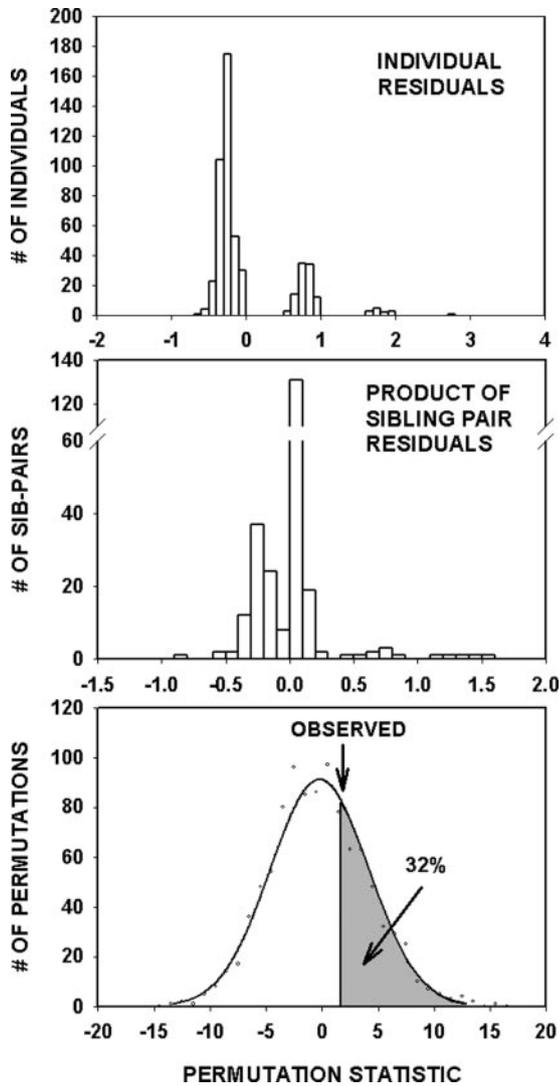


FIG. 2. Analysis of concordance in the 251 sibling pairs using thyroid cancer, hyperparathyroidism, salivary neoplasms, and neural tumors in the analysis. The top panel shows individual residuals, as defined in *Subjects and Methods*, for the 502 subjects in the study. The distribution is explained by the fact that the number of tumors any individual had was zero, one, two, three, or four, and from this, the expected value for each tumor, a positive number, was extracted. The sum of the values is zero, i.e. the expected number of tumors equals the observed number. The middle panel shows the distribution of the products of the residuals. Values greater than zero indicate a concordant sibling pair (i.e. the product of two positive or two negative values). The sum of the products is the observed concordance score for the population and is shown by the vertical arrow, labeled “observed,” in the bottom panel. The bottom panel shows that the observed population concordance score was larger than 68% of the scores generated by random permutations (i.e.  $P = 0.32$ ).

Could biases in the reporting of data to the study or in the intensity of medical attention received by the participant account for the findings? Although these factors cannot be discounted, it is expected that they would account for increased, rather than decreased, concordance. If one sibling develops a radiation-related neoplasm, it would be more likely that the other sibling would have a heightened awareness of the risk and would seek medical attention. Also, when one sibling provides information to the study, it facilitates

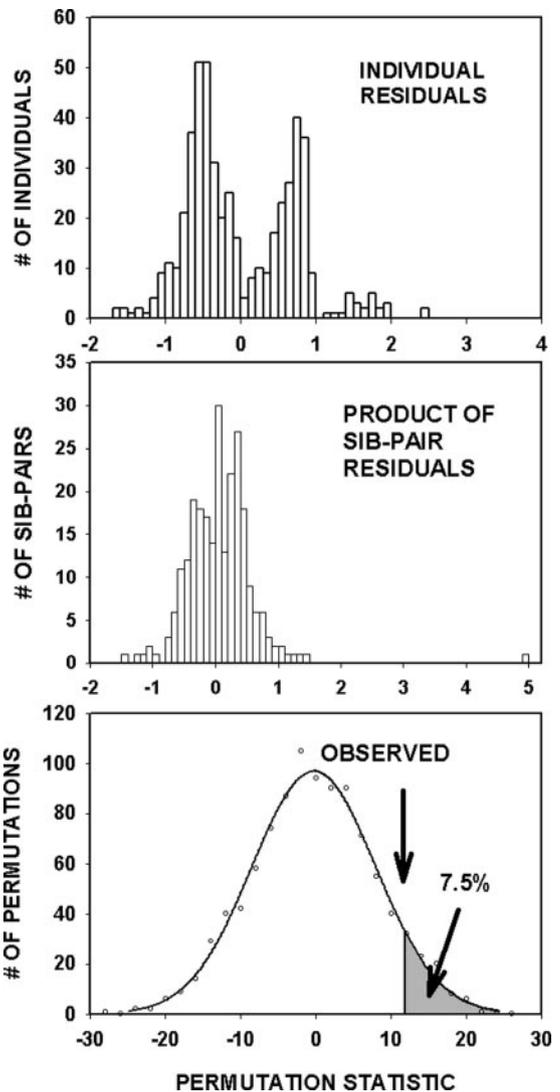


FIG. 3. Analysis of concordance in the 251 sibling pairs as described in Fig. 2, except using thyroid nodules (as defined in *Subjects and Methods*), including thyroid cancer in the analysis. The observed population concordance score was larger than 92.5% of the scores generated by random permutations (i.e.  $P = 0.075$ ; bottom panel).

TABLE 3. Intrafamilial correlations of residuals by ANOVA for models using thyroid cancer (left) and thyroid neoplasms (right) as components of the end points

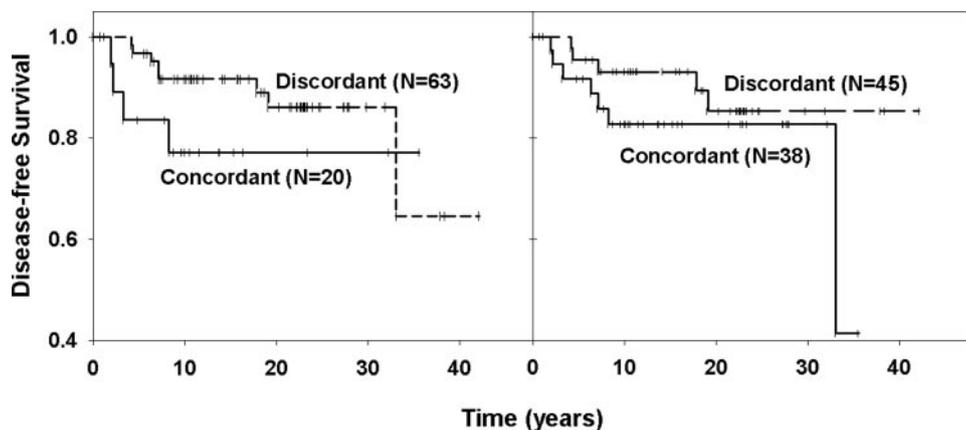
	df	Mean square	Significance	Mean square	Significance
Between-family	250	0.288	0.350	0.575	0.076
Within-family	251	0.273		0.478	
Intraclass correlation		0.024		0.091	

obtaining information from the other sibling, again increasing the chance of observing concordance. Other factors could contribute to concordance. Radiation-associated thyroid cancer may be more common in Jews, and most of the individuals in this cohort are Jewish. However, our information about religion is incomplete, so an analysis taking this into account was not possible. Family history and shared environment could also contribute to concordance, but would be expected to increase, rather than decrease, it.

**TABLE 4.** Characteristics of the 83 thyroid cancers, categorized according to the presence or absence of radiation-related neoplasms (parathyroid, neural, salivary, and either thyroid cancer or thyroid nodules, including cancer) in the sibling

	All siblings	Siblings with thyroid cancer	End points include thyroid cancer		End points include all nodules	
			Concordant	Discordant	Concordant	Discordant
No. in group	502	83	20	63	38	45
Age at Rx (yr)	4.0 ± 2.6	3.7 ± 2.8	4.5 ± 3.0	3.4 ± 2.6	3.9 ± 3.0	3.50 ± 2.6
Gender (% male)	59.7 (300 of 502)	50.6 (42 of 83)	50.0 (10 of 20)	50.7 ± (32 of 83)	57.8 (22 of 38)	44.4 (20 of 45)
Thyroid dose (cGy)	63.0 ± 31.3	65.6 ± 39.8	58.1 ± 21.0	67.9 ± 44.0	69.7 ± 49.5	62.1 ± 29.5
Age at Sx (yr)		30.9 ± 10.1	31.7 ± 13.0	30.6 ± 9.1	30.9 ± 11.3	30.9 ± 9.1
Latency (yr)		27.23 ± 9.2	27.2 ± 11.3	27.2 ± 8.6	27.0 ± 10.1	27.4 ± 8.6
Size (mm)		15.0 ± 11.1	11.1 ± 7.4	15.2 ± 11.8	12.2 ± 11.5	15.1 ± 16.7
Lymph nodes (% present)		40.0 (32 of 80)	44.4 (8 of 18)	38.7 (24 of 62)	41.6 (15 of 36)	38.6 (17 of 44)
Multicentricity (% present)		59.5 (47 of 79)	52.9 (9 of 17)	61.2 (38 of 62)	57.1 (20 of 35)	61.3 (27 of 44)
Bilaterality (% present)		26.6 (21 of 79)	35.2 (6 of 17)	24.1 (15 of 62)	34.3 (12 of 35)	20.5 (9 of 44)
Benign nodules (% present)		60.3 (47 of 78)	50.0 (8 of 16)	62.9 (39 of 62)	50.0 (17 of 34)	68.2 (30 of 44)

FIG. 4. Recurrence of thyroid cancers according to the presence or absence of one or more radiation-related neoplasms in the sibling. Disease-free survival, shown by Kaplan-Meier plots, is shown. For the *left panel*, concordance includes thyroid cancer in the sibling, whereas in the *right panel* concordance includes thyroid nodules, including cancer in the sibling. The characteristics of the thyroid cancers included in each of the four plots are shown in Table 4.



Using cancer as the thyroid-related end point had the advantage of being unambiguous. In these analyses, there was no evidence of a susceptibility effect, and the estimated (nonsignificant) risk ascribable to family factors was only 2.4% (intra-class correlation). In an earlier study, we found more support for concordance when thyroid nodules, including cancer, were considered as the end point (15). However, as in the initial observations more than 15 yr ago, we have recognized, with the use of ultrasound examinations, that about 90% of the subjects in this study have thyroid nodules (16). Therefore, we adopted the criteria described above to include only the larger and potentially clinically significant benign nodules. Although there is some support for excess concordance in these analyses, with an ascribable risk of 9.1%, the findings are not statistically significant. It should be noted that in addition to the large number of tumors that accumulated in the intervening 15-yr interval, the current analysis uses specific organ-dose exposure estimates that were not available for the earlier study.

There is good reason to expect that there are genetic radiation susceptibility factors (19). The syndrome of ataxia telangiectasia, caused by a recessive mutation in the ATM gene, includes a marked increase in radiation sensitivity. It is estimated that about 1% of the general population is heterozygous for ATM mutations. ATM plays a central role in the response to radiation damage, either promoting apopto-

sis or facilitating DNA repair. There is some evidence, based on a small number of cases, that heterozygous women are at increased risk for radiation-related breast cancer (20). Polymorphisms in the genes directly active in DNA repair, presumably producing small quantitative changes in function, are candidates for producing variations in radiation susceptibility (12). Evidence supporting this concept comes from epidemiological studies of patients who develop second cancers after treatment of a first one (21, 22). Information about cancer and other neoplasms in first degree relatives (especially parents and siblings) not exposed to radiation will be obtained in the future, as these may shed additional light on genetic susceptibility factors.

In considering radiation susceptibility, it is tempting to assume that exposed individuals who develop tumors are more susceptible than similarly exposed individuals who do not. However, if this were true, it would be expected that an individual who develops one tumor would be more likely to develop a second. We did not find this, as reported previously (14). Similarly, it is often assumed that susceptibility has a genetic component. If this were true, then concordance in exposed sibling groups would exceed what is predicted based on known risk factors. Again, we did not find this. Thus, it appears that although radiation has been a potent carcinogen in this group, it has acted rather randomly.

The findings show the difficulty in assigning a suscepti-

bility phenotype and the associated difficulty of testing candidate susceptibility genes. Our hypothesis and analyses are related to general radiation susceptibility factors. It remains possible that there are organ-specific factors, but given the smaller numbers, these will be even more difficult to find. Even with pan-genomic methodology, the uncertainty about what phenotype represents increased susceptibility needs to be taken into account. The findings do not exclude subtle variations in susceptibility that could only be detected in larger cohorts, by case-control studies, or by multigeneration pedigree studies.

A secondary goal of the present study was to determine whether there were any differences in the presentation or clinical behavior of the thyroid cancers in patients with siblings affected by radiation-related neoplasms compared with patients whose siblings did not have radiation-related neoplasms. Among the presenting characteristics, age at surgery and latency (years from radiation exposure to surgery) are of interest because one might expect cancers in individuals with increased susceptibility to occur at younger ages and with shorter latency. This was not seen. With respect to behavior, the tendency for concordant cancer to recur more quickly was not significant. Therefore, there is no reason to expect a different outcome or to alter the management of thyroid cancer based on the tumor status of an irradiated sibling.

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### References

- Schneider AB, Ron E, Lubin J, Stovall M, Gierlowski TC 1993 Dose-response relationships for radiation-induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on the thyroid. *J Clin Endocrinol Metab* 77:362–369
- Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice Jr JD 1995 Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 141:259–277
- Schneider AB, Ron E 2000 Thyroid diseases: tumors: carcinoma of follicular epithelium: pathogenesis. In: Braverman LE, Utiger RD, eds. *Werner-Ingbar's the thyroid*, 8th Ed. Philadelphia: Lippincott Williams & Wilkins; 875–886
- Fujiwara S, Sposto REH, Akiba S, Neriishi K, Kodama K, Hosoda Y, Shi-maoka K 1992 Hyperparathyroidism among atomic bomb survivors in Hiroshima. *Radiat Res* 130:372–378
- Ron E, Modan B, Boice Jr JD, Alfandary E, Stovall M, Chetrit A, Katz L 1988 Tumors of the brain and nervous system after radiotherapy in childhood. *N Engl J Med* 319:1033–1039
- Land CE, Saku T, Hayashi Y, Takahara O, Matsuura H, Tokuoka S, Tokunaga M, Mabuchi K 1996 Incidence of salivary gland tumors among atomic bomb survivors, 1950–87. Evaluation of radiation-related risk. *Radiat Res* 146:28–36
- Schneider AB, Lubin J, Ron E, Abrahams C, Stovall M, Goel A, Shore-Freedman E, Gierlowski TC 1998 Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose-response relationships. *Radiat Res* 149:625–630
- Sznajder L, Abrahams C, Parry DM, Gierlowski TC, Shore-Freedman E, Schneider AB 1996 Multiple schwannomas and meningiomas associated with irradiation in childhood. *Arch Intern Med* 156:1873–1878
- Schneider AB, Gierlowski TC, Shore-Freedman E, Stovall M, Ron E, Lubin J 1995 Dose-response relationships for radiation-induced hyperparathyroidism. *J Clin Endocrinol Metab* 80:254–257
- Gatti RA 2001 The inherited basis of human radiosensitivity. *Acta Oncol* 40:702–711
- Geoffroy-Perez B, Janin N, Ossian K, Lauge A, Croquette MF, Griscelli C, Debre M, Bressac-de-Paillerets B, Aurias A, Stoppa-Lyonnet D, Andrieu N 2001 Cancer risk in heterozygotes for ataxia-telangiectasia. *Int J Cancer* 93:288–293
- Mohrenweiser HW, Jones IM 1998 Variation in DNA repair is a factor in cancer susceptibility: a paradigm for the promises and perils of individual and population risk estimation? *Mutat Res-Fundam Mol Mech Mut* 400:15–24
- Smith TR, Miller MS, Lohman K, Lange EM, Case LD, Mohrenweiser HW, Hu JJ 2003 Polymorphisms of XRCC1 and XRCC3 genes and susceptibility to breast cancer. *Cancer Lett* 190:183–190
- Mihailescu D, Shore-Freedman E, Mukani S, Lubin J, Ron E, Schneider AB 2002 Multiple neoplasms in an irradiated cohort: pattern of occurrence and relationship to thyroid cancer outcome. *J Clin Endocrinol Metab* 87:3236–3241
- Perkel V, Gail MH, Lubin J, Pee D, Weinstein R, Shore-Freedman E, Schneider AB 1988 Radiation-induced thyroid neoplasm: evidence for familial susceptibility factors. *J Clin Endocrinol Metab* 66:1316–1322
- Schneider AB, Bekerman C, Leland J, Rosengarten J, Hyun H, Collins B, Shore-Freedman E, Gierlowski TC 1997 Thyroid nodules in the follow-up of irradiated individuals: comparison of thyroid ultrasound with scanning and palpation. *J Clin Endocrinol Metab* 82:4020–4027
- Cox DR 1972 Regression models and life tables. *J R Stat Soc* 34:187–220
- Snedecor GW, Cochran WG 1967 Statistical methods. Ames: Iowa University Press; 294
- Sankaranarayanan K, Chakraborty R 1995 Cancer predisposition, radiosensitivity and the risk of radiation-induced cancers. I. Background. *Radiat Res* 143:121–143
- Swift M, Morrell D, Massey R, Chase C 1991 Incidence of cancer in 161 families affected by ataxia-telangiectasia. *N Engl J Med* 325:1831–1836
- De Vathaire F, Hardiman C, Shamsaldin A, Campbell S, Grimaud E, Hawkins M, Raquin M, Oberlin O, Diallo I, Zucker JM, Panis X, Lagrange JL, Daly-Schweitzer N, Lemerle J, Chavaudra J, Schlumberger M, Bonaiti C 1999 Thyroid carcinomas after irradiation for a first cancer during childhood. *Arch Intern Med* 159:2713–2719
- Kony SJ, De Vathaire F, Chompret A, Shamsaldin A, Grimaud E, Raquin M, Oberlin O, Brugieres L, Feuteun J, Eschwege F, Chavaudra J, Lemerle J 1997 Radiation and genetic factors in the risk of second malignant neoplasms after a first cancer in childhood. *Lancet* 350:91–95