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Risk of Thyroid Neoplasms after Irradiation in Childhood

Studies of populations exposed to radiation in childhood show a dose response over a wide dose range.

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Until relatively recently, the thyroid gland has been classified as a radioreistant organ (1). This classification was based on the fact that large doses of radiation are needed to depress secretory function and to produce histological evidence of tissue damage. Recent studies of late radiation effects indicate that, under certain conditions, neoplastic transformation of the gland can be initiated by radiation doses lower than those formerly considered to be damaging to tissues (2). With respect to this type of radiation damage, the thyroid should be regarded as one of the more radiosensitive organs in the body. This radiosensitivity was not recognized earlier because such radiation injury leading to

the subsequent development of grossly apparent neoplasms is not apparent unless the damaged thyroid cells proliferate for many cell generations. Because parenchymal cells divide only infrequently in the normal adult gland, conditions are unfavorable for the expression of cellular damage induced by radiation. However, in children whose glands are proliferating rapidly (2) or in adult animals with glands stimulated by goitrogens (3) the cells injured by radiation and with abnormal growth potential are able to develop into gross neoplastic lesions. The radiosensitivity of the growing thyroid glands of children is of interest because of the potential exposure of large segments of

the world's population to radioactive iodine in the fallout from nuclear testing or from accidents with nuclear reactors.

Risk of Malignant Transformation after Radiation Exposure

Attempts to obtain an accurate estimate of man's chance of developing thyroid neoplasms after exposure to radiation have been hampered by three uncertainties. (i) Information about the dose response is unsatisfactory because data on incidence of thyroid neoplasms in man after exposure to different doses are limited. (ii) The radiation doses to the thyroid gland used in calculations of risk may be questioned in most studies dealing with children given x-ray treatments to the chest or neck. In these instances, the dose to the thyroid was derived from the x-ray dose in air without taking into account whether the gland was inside or outside the primary beam. In that the radiation dose in tissues falls rapidly at the periphery of the x-ray beam, the location of the gland with respect to the beam is usually more important in determining the thyroid dose than the dose in air is. (iii) The criteria used in diagnosing malignancy were not always uniform. However, because of the need to assess

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the hazards involved in exposure of the thyroid to radiation, calculations of the risk have been made with the best clinical material available and with reasonable assumptions to take into account the above uncertainties. In these calculations, it has been assumed that the dose response is linear, that the thyroid glands were in the primary beam, and that the published histological diagnoses are correct.

Beach and Dolphin (4) made the first estimate of the risk of developing thyroid carcinomas after exposure to radiation. Their calculations were based on pooled data from three published surveys of the incidence of neoplastic disease in persons given x-ray treatments to the chest or neck in infancy or childhood. They assumed that the glands were always in the primary beam and converted dose in air to dose to the thyroid gland by correcting for absorption of the x-rays in the tissues overlying the gland. When the incidence of thyroid cancer in the exposed children was plotted as a function of the estimated thyroid dose, the best fit to the points was a straight line with a slope of 1.7 percent incidence of thyroid cancer per 500 rad (thyroid dose). Assuming that the linear relationship between dose and effect is correct, they estimated that the risk of developing thyroid cancer was 35 per 10^6 persons exposed per rad. Because they considered that a period of 20 years after irradiation was the time during which all but occasional thyroid malignancies occur, the risk per 10^6 persons per rad per year became 1.75.

In the *Report of the United Nations Scientific Committee on the Effects of Atomic Radiations* (UNSCEAR) on radiation carcinogenesis in man (5), the risk of developing thyroid cancer was calculated with data from six surveys of thyroid carcinoma in populations irradiated as infants or children. The doses in air recorded in the surveys were used without correction to approximate the doses to the thyroid. The mean follow-up period after irradiation was 16 years. The mean risk for all groups was 0.9 case per 10^6 persons per rad per year, with 0.5 and 1.5 cases per 10^6 persons per rad per year as the approximate confidence limits. That report emphasizes the fact that the estimate would be valid only for persons irradiated as children with x-rays in the dose range of 100 to 300 rad. Three factors probably account for the discrepancy between this risk value and

that of Beach and Dolphin: (i) the latter study was based on fewer data than the UNSCEAR report; (ii) in the latter report, the rad dosage of the glands was reduced by correcting for tissue absorption of the x-rays; and (iii) Beach and Dolphin introduced a correction factor to take into account the inadequate follow-up period in some studies.

With my co-workers (2), I attempted to refine the risk estimate for radiation-induced thyroid carcinoma in the Rochester series of persons irradiated as infants because of alleged thymic enlargement. We used values for the estimated thyroid dose which took into account both tissue absorption of x-rays and the spatial relationship of the gland to the beam in each individual case. We estimated a risk of approximately 2.5 cases per 10^6 per rad per year for the total irradiated population with a mean follow-up of 17 years. This value was not altered when we considered only persons who had received thyroid doses estimated to be either below or above 100 rad or those in the oldest cohort (over 23 years of age) or in the oldest two cohorts (over 13 at the time of the study). These risk values apply only to persons irradiated with x-rays in childhood.

New Data on Risk of Thyroid Neoplasms

Within the past 2 years, three studies (6-8) reported the incidence of nodular thyroid disease in persons exposed to ionizing radiation in childhood. Two of these studies (7, 8) primarily provide information on clinically detectable thyroid nodules in irradiated populations. Because biopsies or excisions were not performed on those lesions believed to be benign, the exact character of the nodules is not known. Nodularity in a previously irradiated gland of a young adult, however, probably represents radiation-induced thyroid disease. As animal experimentation (9) and experience in man (2, 7, 8) have shown, the lesions in such irradiated glands begin as focal hyperplasia and develop into adenomas or carcinomas. By considering thyroid nodularity rather than carcinomas only, we are able to increase the dose range of case material available for analysis.

Repeat study of the 1965 Ann Arbor series (6). Latourette and Hodges (10) published the results of a mail survey

of the incidence of thyroid neoplasms in a group of 958 persons treated for thymic enlargement in infancy. One treatment was given to 758 of these persons. The average dose of x-rays in air was 200 roentgens, and the usual treatment field measured 10 by 10 centimeters. According to the radiologists who gave the treatments, the necks of the children—and therefore the thyroid glands—were not in the primary x-ray beam; therefore, the average thyroid dose of scattered x-rays was of the order of 20 rad (2). Latourette and Hodges observed one case of thyroid carcinoma, whereas 0.06 case was expected on the basis of cancer rates in the general population. No benign thyroid tumors were reported.

Six years later, my co-workers and I repeated the mail survey for the 786 persons still available for study; the mean age of this population at this time was 29 years (6). We identified seven new surgically excised thyroid adenomas but no additional cases of carcinoma. The ratio of observed to expected cases of carcinoma was 1:0.13, and that for adenomas was 7:1.3. As age-specific rates of benign tumors in the general population were not available, the latter value for expected number of adenomas is based on the ratio (1:10) of malignant to benign tumors found in surgical specimens of a large tumor registry (2). We concluded that the incidence of surgically removed thyroid tumors—eight in 758 subjects or 1.1 percent—was higher than that expected in a comparable nonirradiated population. With the ratio (3:1) of clinically palpable nodules to surgically removed thyroid tumors noted in the Rochester study (discussed below), the incidence of thyroid nodularity in this population would be of the order of 3 percent, whereas that for carcinoma was 0.13 percent.

Examination of high-risk subgroup C in the Rochester series (7). During a 10-year period, repeated mail surveys of the Rochester series of almost 3000 persons treated for thymic enlargement identified a subgroup of 268 individuals with a particularly high risk of developing thyroid and other neoplasms [ten carcinomas and ten adenomas of the thyroid (2)]. These individuals, designated as subgroup C, had been treated during infancy in one radiologic facility with a mean dose in air of 383 roentgens. There is good evidence that the treatment fields were large enough to permit the thyroid glands of the infants

to be irradiated by the primary x-ray beam; this means that mean estimated dose to the thyroid was approximately 335 rad. Opposing anterior and posterior treatments were given on the same day. An anterior and posterior exposure was administered in 1 day to each of 104 infants; in 164 others, the total dose was divided into two or more treatments usually given at intervals of 2 weeks.

The information concerning thyroid tumor incidence in subgroup C obtained by mail survey was supplemented (7) by additional data from examination of those individuals still residing in the Rochester area. Two thyroid specialists examined 105 persons; each subject had reported no thyroid abnormality on the previous mail questionnaire in 1963. In the same way, they studied 116 non-irradiated controls matched for sex, age, and place of residence. On the initial examination of these individuals ranging in age from 17 to 35 years, 23 nodular thyroid glands were palpated in the irradiated group in contrast to two in the matched, nonirradiated control group. Five lesions suspected of being malignant proved to be benign when the surgically excised tissues were examined; all others were considered to be benign on the basis of clinical diagnosis. Except for minor changes in the protein-bound iodine of two female patients and a mild depression of radioactive iodine uptake of one male, there was no clinical evidence of thyroid dysfunction in any of the examined subjects.

With the assumption that the same incidence of thyroid nodularity prevailed in the examined and unexamined persons who reported no thyroid disease and with the addition of the 44 cases so obtained to the 20 lesions known to have been removed surgically, an incidence of 28 percent nodularity was projected for the 235 living persons in the high-risk group (7). A ratio of approximately three clinically palpable nodules for every one removed surgically was thereby obtained. The ten cases of thyroid carcinoma revealed by mail questionnaire (2) and proved by histological study gave an incidence of 4.3 percent.

Marshallese children exposed before age 10 to radiation from fallout from nuclear test (8). In 1954, 19 children under 10 years of age on Rongelap Island in the South Pacific were exposed to radiation from the fallout of fission products from a nuclear test on nearby Eniwetok Island (8). Their thyroid

glands were irradiated both by γ -rays from fission products deposited on the Island and by β - and γ -rays from ingested radioactive isotopes of iodine temporarily stored within the glands. The dose to the thyroid from external γ -rays was estimated to be of the order of 175 roentgens in air, whereas that from ingested iodine was computed to be in the range of 700 to 1400 rad (depending in part on the age of the child and the size of the gland during exposure).

Within 12 years after exposure, 15 of the 19 persons had developed nodular thyroids with an incidence of 78 percent. Histological examination of the five excised lesions revealed benign multiple adenomas or focal hyperplasia; the other thyroid nodules were also diagnosed clinically as benign. Two children suffered from complete myxedema, and four others showed evidence of a reduced thyroid reserve. In 1965, levothyroxine was prescribed for the more heavily exposed persons to treat the unexcised nodules and to prevent development of new lesions.

Nonirradiated control populations. Data on the incidence of nodular thyroid glands in nonirradiated populations comparable in age to the irradiated groups are not entirely satisfactory. The incidence of lesions as determined by mail survey of the nonirradiated siblings of the Rochester thymus-irradiated children (2) should serve as a good control, particularly for the Ann Arbor series, because the method of data collection was identical in both studies. In 2508 Rochester siblings 15 years or older (average age, 22.5 years), three surgically excised adenomatous lesions were reported with an incidence of 0.12 percent [recalculated from crude data in (2)]. With 3:1 as the ratio of surgically excised lesions to palpable nodular glands, the probable incidence of nodularity becomes 0.36 percent. In the 116 nonirradiated controls matched for age, sex, and place of residence with subgroup C of the Rochester series (7), two nodular glands were detected; this gave an incidence of 1.7 percent. When we consider the relatively young age of the controls (17 to 35 years) and the tendency of thyroid nodularity to occur predominantly in older people, this value of 1.7 percent seems to be higher than that expected on the basis of other studies of larger populations containing older subjects. In the Framingham study of persons in the general population be-

tween the ages of 30 and 59 years (11), the incidence of nodularity on the initial examination was 1.6 percent. In the survey of persons of all ages in Tecumseh, Michigan (12), the incidence of palpable nodules was 0.47 percent, and that of surgery for goiter (whether it was nodular or not was not specified) was 0.65 percent. Most of the nodular glands occurred in older people.

In the absence of better information, we shall consider the incidence of clinically palpable nodular glands in non-irradiated populations (comparable in age to the irradiated study groups) to be between the extremes of 0.36 percent (possibly low because of the method of data collection) and 1.7 percent (possibly high because of the small sample size of the matched Rochester controls).

Estimates of the Risk of Developing Thyroid Neoplasms

It is apparent from the data in Fig. 1 that the dose response is approximately linear. In the thyroids of the Marshallese children, the dose used in the calculation is the sum of the mid-dose of 1050 rad of β -rays from radioiodine and 175 roentgens of external γ -rays. Whether β -rays emitted at a slow dose rate are as effective in inducing thyroid tumors as x-rays administered at a fast rate is debatable (13); this means that the biologically effective dose in the Marshallese may be different from the physical dose. If radioiodine is less oncogenic than x-rays in man (as it is in rats), the point of incidence for Marshallese should be shifted far to the left; than the plot of the response as a function of this biologically effective radiation dose becomes curvilinear. Because the follow-up period is so short (14 years), it also seems quite likely that the ultimate incidence value would increase with time; in view of the prophylactic treatment of these persons with thyroxine, however, this may never occur. The protraction of the treatments in many of the Rochester children may also have reduced the biological efficacy of the total dose; if this is so, then this incidence point should also be moved to the left. Analysis of the data in the Rochester series, however, gives no indication that this is the case. Although lower doses were usually given as single exposures and higher doses as multiple treatments, there is considerable over-

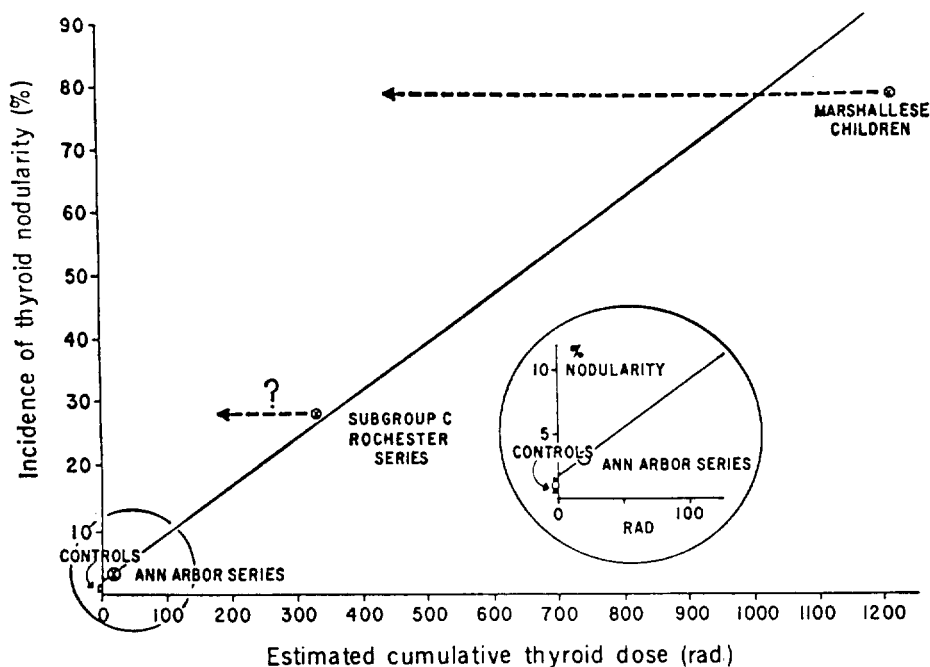


Fig. 1. Incidence of thyroid nodularity in relation to estimated cumulative dose to the thyroid gland. The points represent values based on real (or assumed) incidence of nodularity and estimated mean cumulative physical doses to the thyroid gland. The horizontal dashed line and arrow represent the direction in which the mean dose of the Marshallese should be adjusted to take into account the fact that β -rays from iodine-131 are probably less effective than x-rays in inducing thyroid neoplasms. Animal experiments indicate that β -radiation is one-tenth to one-fifteenth as effective as x-irradiation (13); this obviously could not be the case here (unless the estimated dose is too small), because a correction of this magnitude would reduce the dose to the Marshallese thyroids to less than that of the subgroup C children. The horizontal dashed line and arrow for subgroup C takes into consideration the possibility that the fractionated doses might be less effective than single exposures—a presumption not substantiated by the evidence at hand.

lap in the category of 300 to 399 rad. Of 44 persons in this category who received single exposures, none had nodular glands, whereas three such lesions occurred in 46 persons given the same total dose in protracted exposures.

With the data given above, the following risks are obtained for the three study groups (on the basis of 10^6 persons per rad per year): (i) in the Ann Arbor series, for thyroid nodularity, $24(10^6/786)(1/20)(1/29)$, or 53 cases, and for thyroid carcinoma, 2.2 cases; (ii) in the Rochester subgroup C, for nodularity, $64(10^6/233)(1/329)(1/24)$, or 38 cases, and for carcinoma, 5.5 cases; and (iii) in the Marshallese, for nodularity, $13(10^6/18)(1/1225)(1/12)$, or 48 cases, and for carcinoma, no cases.

Comments

The apparent linearity of the dose response for radiation-induced thyroid nodularity over the range of 20 to 1125 rad (thyroid dose), the small variation in the risk of developing nodules over

this wide dose range and the presumed lack of a threshold are the surprising results obtained in this analysis. If it is true, however, that the β -radiation dose to the Marshallese glands was less efficient than the same dose of x-rays in inducing nodularity, then the use of cumulative physical dose in making these comparisons is misleading. Substitution of the biologically effective dose of the β -radiation, if it were known, for the physical dose in this study would probably result in a curvilinear dose response in the higher dose range. It would also lead to a considerably higher value for the risk of nodularity in the Marshallese than the estimated value of 48 cases per 10^6 per rad per year.

Because of the limited number of cases of carcinoma in the three studies, we can say little about the dose response of radiation-induced malignant lesions. That the risk value of 2.2 cases of carcinoma per 10^6 per rad per year in the Ann Arbor series should be so close to previous estimates is perhaps fortuitous since the estimate is based on one case. The risk value of 5.5

carcinomas per 10^6 per rad per year for the Rochester series, although higher than those previously proposed, may well be the most valid of all, because this subgroup has been more carefully studied than the populations surveyed by mail only and the dose estimates are probably more accurate.

The values given represent average values for the first 25 years or so of life and are valid only if the exposures occurred during childhood or infancy. Radiation-induced carcinomas of the thyroid rarely occur before age 10, increase rapidly in incidence in the teens, and level off or probably decrease in frequency in the twenties (2). Because the incidence of thyroid cancer is not linear with age, the actual risk before age 10 and after age 20 should be lower than 2.5 to 5.5 cases per 10^6 per rad per year, whereas that during the teens will be higher than these values.

The increased incidence of thyroid nodularity in the Ann Arbor study is remarkable in view of the small doses of scattered radiation believed to have been received by the glands. This suggests that there may not be a threshold for this response or that, if there is a threshold, it is below 20 rad. Previously, in man the lowest dose believed to be oncogenic was 75 to 100 rad of total body radiation. This is the dose estimated for some Japanese with an increased incidence of leukemia after exposure to the nuclear detonations in 1945 (14). In female rats of the Sprague-Dawley strain studied for 1 year after irradiation with x-rays, however, total body exposure to x-ray doses as low as 25 rad caused an increase in the incidence of mammary carcinomas (15). Also, in female mice irradiated with 32 rad, the lifelong incidence of ovarian tumors was increased (16).

Whether the dose response is linear or curvilinear has an important bearing on our understanding of the mechanisms of neoplastic transformation of the irradiated gland. If the response is truly linear, then the nodules in the lightly exposed Ann Arbor group (presumably without functional thyroid damage) must have developed in exactly the same way as those in the more heavily exposed Marshallese (some of whom suffered thyroid damage). This suggests that a single event, perhaps a radiation-induced mutation, could be responsible for the development of the neoplasms without regard to the functional capacity of the thyroid or the thyroid-pituitary axis.

The following observations, however, suggest that pathogenesis of the neoplastic lesions is not the result of a single event and that factors other than radiation function in the neoplastic transformation. (i) There is no relation between the magnitude of the dose and the latent period between exposure and the development of thyroid neoplasms (2). (ii) There is a poor correlation between the magnitude of the dose and the stage of the neoplastic process, that is, whether it is malignant or benign (2). (iii) Some data suggest that thyroid cancer develops at the same time in life regardless of whether irradiation occurred in infancy or later in childhood (6). The fact that more than one factor seems to play a part in the induction of thyroid neoplasms is consistent with the multistage theory of carcinogenesis in endocrine glands (9). In radiation-induced neoplasms of the thyroid, the primary event is radiation damage of thyroid cells (presumably chromosomal in nature); from the rapid increase in incidence of the lesions during the teens, the secondary or promoting event could well be thyroid stimulation during adolescence (2).

In that the thyroid is under pituitary control (by a feedback mechanism involving secretion of a thyroid-stimulating hormone), any deficiency in thyroid function serves to stimulate this secretion, and this promotes neoplastic transformation of the radiation-damaged cells (9). Therefore, we conclude that the pathogenesis of the thyroid nodules in the Marshallese was not apt to be the same as that in the Ann Arbor series and that the single-event hypothesis mentioned above is probably incorrect.

If this evidence against the single-

event hypothesis is added to that concerned with the probable reduced efficiency of β -rays in inducing neoplastic transformation in the Marshallese, then the linear dose response based on cumulative physical dose is misleading. In the high-dose range where thyroid functional capacity has been damaged, it seems likely that the biologically effective dose response is curvilinear. In the low-dose range, however, the response could well be linear, as indicated in Fig. 1.

Summary

The incidence of thyroid carcinoma and of clinically palpable thyroid nodules is compared in three groups of individuals many years after exposure to ionizing radiation in childhood or infancy. The estimated mean cumulative doses to the thyroid gland ranged from 20 rad in the Ann Arbor series irradiated with x-rays as infants for thymic enlargement upward to 1225 rad of mixed radiation (including that from ingested radioiodine) in the Marshallese children. Intermediate between these extremes is the high-risk subgroup in the Rochester series of persons irradiated for thymic enlargement; they received an estimated mean thyroid dose of 335 rad.

A plot of the incidence of thyroid nodularity against the total cumulative thyroid dose gives what could be a linear dose response with no threshold or, at least, a threshold below 20 rad. The risk of developing carcinoma in the three studies ranges from 0 to 5.5 cases and that for nodularity 38 to 52 cases per 10^6 persons exposed per rad

(thyroid dose) per year. There is evidence from animal experimentation that the biologically effective dose in the case of the Marshallese would have been considerably lower than the cumulative physical dose; hence, the dose response might actually be curvilinear at least in the higher dose range.

In view of the uncertainties regarding dose and the assumptions made in my study, the risk values may not be exact; however, these values reflect the trends regarding risks estimated from the best available data in man. Furthermore, the estimated risk values apply only if radiation exposure occurred in childhood.

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