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Radiation-induced thyroid neoplasia

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The possibility that thyroid cancer can be induced by ionizing radiation was first suggested in 1949 by Quimby and Werner[1]. One year later, Duffy and Fitzgerald[2] proposed that X-ray treatment could to some extent be responsible for the development of thyroid cancer in children and adolescents in the United States. In 1955, Simpson et al.[3] reported a high incidence of thyroid neoplasms in a population of X-irradiated young adults. Thyroid carcinoma was also the first solid malignant tumor observed to be on the increase among the Japanese atomic bomb survivors[4]. These studies have since then been followed by many others, and the etiologic role of ionizing radiation in the development of thyroid neoplasms is now well established.

Experimental studies on radiation-induced thyroid cancer

The thyroid has been a unique model in experimental studies on radiation carcinogenesis for several reasons: the gland has the capacity to concentrate iodine, thyroid cell proliferation can be manipulated, and thyroid hormones can be measured[5,6].

Thyroid carcinogenesis has therefore been extensively studied in experimental animals. The factors that appear to be involved are (a) initiation of carcinogenesis by e.g. ionizing radiation and (b) promotion of carcinogenesis, i.e. an event of reversible stimulation of thyroid cells to proliferate. The stimuli may be goitrogens, thyroid stimulating hormone (TSH) or lack of dietary iodine.

Ionizing radiation is still the only known initiating factor in thyroid carcinogenesis, and has therefore played an important role in experimental studies of thyroid cancer induction[5–10]. The fact that ^{131}I accumulates in the thyroid gland has frequently been exploited in experimental induction of thyroid tumors in rats and mice. Earlier studies with high radiation doses to the thyroid gland suggested that ^{131}I was one-tenth to one-fourth as effective as X-rays in producing tumors[10–12]. This difference has been ascribed, at least in part, to the non-uniform dose distribution of ^{131}I in the thyroid gland. Microdosimetric inhomogeneities may also be important, so that functioning thyroid follicles receive a much higher radiation dose than do non-functioning follicles. This is considered to be one possible explanation why ^{125}I has a greater biologic effectiveness than ^{131}I[13]. Walinder et al.[10] observed that ^{132}I had the same effect on the thyroid gland in mice measured as inhibition of goitrogen-stimulated growth as equivalent doses of X-rays, whereas ^{131}I had a much weaker effect. The authors concluded that the observed difference in radiation damage was mainly due to differences in dose rates. The reported optimal thyroid radiation doses for cancer induction in rats and mice are 5–10 Gy of X-rays or 100–150 Gy of mainly beta rays from ^{131}I[8,11,12].

Contrary to this conclusion, Lee et al.[14] observed that the cancer risk per rad was similar for both radiation types in a study of 3000 Long-Evans female rats that received various radiation doses to the thyroid from X-rays or ^{131}I. Like those of many other animal experiments, their results are limited by the fact that ^{131}I is an efficient cancer inducer only in certain animal species and strains, such as CBA mice and Long-Evans rats. Lee et al. used female Long-Evans rats in their study, and the results might well have differed had male rats or both sexes been used.

Anti-thyroid drugs, such as thionamide compounds, can induce thyroid adenomas and carcinomas in animals if administered over a sufficiently long period[15]. The underlying mechanism for this is believed to be mediated through an increased TSH production rather than by a direct carcinogenic effect on thyroid cells. TSH may thus act as a promoting factor in thyroid radiation carcinogenesis[16]. A lack of dietary iodine also increases the incidence of thyroid tumors in experimental animals and the mechanism for the tumor induction appears to be the same as the mechanism associated with goitrogens, i.e. an increased TSH production. Similarly, thyroid tumors can be induced in animals by subtotal thyroidectomy or by continuous stimulation of the thyroid gland by TSH-producing tumors[17–19]. Hormones generally stimulate tumor growth in cells in which they normally have a mitosis-stimulating effect. The administration of thyroid hormone will suppress TSH secretion, thereby possibly preventing or delaying the development of neoplasms following exposure of the thyroid gland to ionizing radiation[20].

The latency period is shortened and the yield of tumors is increased when X-rays or ^{131}I, acting as initiators, are combined with any of the promoting factors[21–23].

There are both morphological and biological differences between thyroid carcinomas in human beings and in experimental animals. Moreover, human populations are heterogeneous whereas experimental animals comprise homogeneous and often inbred populations living under standardized conditions. Some of the factors suspected to be carcinogenic in man have been shown to induce carcinomas in these animals. Even though the data may not be directly transferable to human beings, they nevertheless contribute to our knowledge about basic mechanisms in the transformation of benign thyroid cells into malignant cells.

Epidemiological studies on radiation-induced thyroid cancer

Epidemiological retrospective surveys on radiogenic cancer in man are generally concerned with a history of exposure several decades ago. In the determination of the absorbed radiation doses there are factors that are difficult to assess retrospectively, such as the irradiated volume and the dose absorbed by the thyroid gland, and whether or not the gland was positioned in the primary beam. Differences in the anatomical contours and small changes in position, especially of children, could have resulted in actual mean thyroid doses several times higher or lower than those estimated.

Another important problem when studying radiogenic thyroid cancer is the fact that the prevalence of malignant thyroid tumors is high even in subjects with clinically normal glands. Serial sectioning of thyroid glands at autopsy has disclosed thyroid cancer in 6–28 % of the glands examined[24–27]. The prevalence in the Japanese and in the Hawaiian Japanese appears to be higher than in the people of Western countries[28]. The prevalence of thyroid cancer increases with the number of histologic slides of the thyroid gland examined[24]. The papillary thyroid cancer detected in serial sectioning of the gland is generally occult, with a diameter of less than 15 mm. The papillary cancer also accounts for a high proportion of the malignant tumors considered to be radiation-induced. Occult thyroid cancers should not be included in estimations of risk associated with ionizing radiation.

The present experience on radiogenic thyroid cancer stems mainly from four types of sources: 1. populations exposed to nuclear explosions, radioactive fallout or high background radiation, 2. patients given radiotherapy for benign conditions, 3. patients given radiotherapy for cancer, and 4. patients exposed to therapeutic or diagnostic ^{131}I doses (Table 1).

Populations exposed to nuclear explosions or fallout

The Japanese population of Hiroshima and Nagasaki exposed to radiation from atomic bombs in 1945

A matched fixed population of approximately 100 000 survivors of the atomic bombs in the two Japanese cities was followed[29, 30], and a significant excess of thyroid cancers for persons exposed to 0.5 Gy or more was observed. The thyroid cancer incidence was higher in females than in males by a factor of about 3. The dose-response appeared to be considerably stronger among persons less than 30 years old at the time of the bombing.

The incidence increased significantly with the thyroid dose, for the non-occult tumors (43 out of 71 thyroid cancers) in Nagasaki, but not for the occult tumors[29]. The autopsy rate of the Life Span Study cohort in Hiroshima was radiation dose-dependent[29], and 43 % of individuals who received

Tab. 1. Types of epidemiologic studies on radiation-induced thyroid cancer.

Type of study (exposure)	Series	Type of control	Reference
Nuclear explosion/ fallout mixed	Nagasaki	Unexposed	29
	Marshall Islands	Unexposed	31, 33
	Utah, Nevada	Unexposed	34, 35
Radiotherapy for benign disorders (X-rays or gamma rays)	Tinea capitis, Israel	Unexposed	40, 41
	Tinea capitis, NY	Unexposed	38, 39
	Thymus, Rochester	Unexposed	42, 44
	Maxon et al.	Unexposed	45
	Schneider et al.	General population	46, 47
	Hemangioma, Sweden	General population + unexposed	49
Radiotherapy for cancer (X-rays or gamma rays)	Cervical cancer	Exposed + unexposed	54
	Pediatric cancer, US	General population	52
	Pediatric cancer, UK	General population	53
Radioiodine (^{131}I)	Hyperthyroidism, US	General population + unexposed	55, 56
	Hyperthyroidism, Sweden	General population	59
	Diagnostic examinations, Sweden	General population	60, 61

Tab. 2. No. of thyroid cancer and No. of thyroid cancers/person-years (PY) at risk classified by sex, age at time of bombing (ATB), city, and total tissue dose[30].

Sex	Age ATB	City	No. of cancers/No. of cancers/PY × 10^6			
			Thyroid dose, Gy			
			0 (n = 54079)	0.01–0.49 (n = 37372)	0.50–0.99 (n = 3297)	1.00 + (n = 3862)
Female	< 30	Nagasaki	4/54	5/62	4/388	12/745
		Hiroshima	11/64	8/81	3/337	2/257
	≥ 30	Nagasaki	5/194	8/215	1/344	0/0
		Hiroshima	13/99	13/164	3/530	2/486
Male	< 30	Nagasaki	2/38	1/17	0/0	4/386
		Hiroshima	3/26	1/14	1/227	0/0
	≥ 30	Nagasaki	2/83	2/99	0/0	0/0
		Hiroshima	2/25	0/0	0/0	0/0

1 Gy or more and who died in the years 1961–1975 were autopsied, whereas only 30% of similar individuals in the 0 Gy dose-group had an autopsy. A similar but less pronounced situation occurred in Nagasaki. It is not clear what effect this has had on the relationsip between thyroid cancer incidence and radiation exposure. Among survivors in both Hiroshima and Nagasaki there were 112 clinically evident thyroid cancers (Table 2)[30], and a clear, predominantly linear relationship between gamma ray exposure and thyroid cancer incidence was observed. After adjustment for dose, the thyroid cancer incidence was two times higher among participants of the Adult Health Study, who had biennial thyroid screening, than among other subjects. The dosimetry has now been revised, and new studies on thyroid cancer incidence in relation to radiation exposure can be expected to appear in the relatively near future.

Marshall Islanders exposed to radioactive fallout from a nuclear bomb test in 1954

These subjects were exposed to external beta and gamma radiation and to internally deposited radionuclides[31]. There were difficulties in estimating the thyroid doses retrospectively. The short-lived radioiodines (^{132}I, ^{133}I, and ^{135}I), with their high dose rate, were estimated to have delivered three times as much radiation to the thyroid glands as did ^{131}I, which has a longer half-life and a lower dose rate. Iodine-131 contributed only about 10–15% of the total thyroid dose[32].

Children were especially sensitive to radiation exposure, and 17 of 22 exposed children less than 10 years of age on Rongelap have developed thyroid nodules. Women were more susceptible to radiogenic thyroid cancer, and all seven thyroid cancers occurred among exposed women as compared to two of the five cases among the controls[33]. The cancer risk was estimated at 1.5×10^{-4} PY Gy^{-1}. For reasons mentioned earlier, the Marshall Islands experience gives no information about the risk that can be attributed to ^{131}I exposure.

Children exposed to radioactive fallout from atomic bomb testing in Nevada

This population consisted of children living in Utah, Nevada and Arizona during the period of weapon testing in the 1950s, and who were exposed to ^{131}I from fallout[34, 35]. No difference in the prevalence of benign and malignant thyroid nodules was found between the 1380 exposed and the 3800 non-exposed subjects. Twelve thyroid nodules were detected in the exposed group (8.7 per 1000 persons) versus 16 nodules among the controls (4.6 per 1000 persons). No thyroid cancer was found among the exposed subjects and two cases were observed among the controls. Accurate determinations of the radiation dose to the thyroid were not available, but the estimated average was 0.46 Gy for the exposed group, with a maximum of 1.20 Gy. The BEIR III[36] used 1.20 Gy as the best estimate. The small sample size, the short follow-up (mean 14 years) and the uncertainty regarding thyroid dose are the major methodological limitations of this study.

Thyroid nodularity after continuous low-dose radiation exposure in China was studied in about 1000 women aged 50–65 years who had resided in areas of high background radiation for their entire lives, and in approximately 1000 comparison subjects exposed to normal levels of radiation[37]. The cumulative doses to the thyroid were estimated to be of the order of 0.14 and 0.05 Gy, respectively. The prevalences of nodular thyroid disease were 9.5% and 9.3%, respectively. The prevalence of single nodules was 7.4% in the high background area and 6.6% in the control area, with a prevalence ratio of 1.13 [95% confidence interval (CI) 0.82–1.55]. The study suggests that continuous exposure to low-level radiation throughout life is unlikely to result in any appreciable increase in the risk of thyroid cancer.

Patients given radiotherapy for benign conditions

Radiotherapy has been widely used to treat a large number of benign conditions such as hemangiomas,

Tab. 3. Radiation dose-response relationship for thyroid cancers and thyroid adenomas following thymus irradiation[44].

	Dose range, Gy (No. of Person-Years)					
	Control (118157)	0.01–0.49 (33449)	0.50–1.99 (6020)	2.00–3.99 (11456)	4.00–5.99 (6382)	≥ 6.00 (1727)
Mean thyroid dose, Gy	0	0.17	1.18	2.54	4.48	7.50
No. of thyroid cancers	1	4	1	6	11	5
Relative risk	0.7	12.9	13.6	45	130	196
No. of thyroid adenomas	8	11	6	12	14	7
Standardized rate ratio	1.0	9.9	18.5	19.7	30.9	36.6

tonsillitis, acne, tuberculous adenitis, ring-worm of the scalp and many others.

Children treated with X-rays for tinea capitis
Two populations have been studied, one in the USA[38,39] and one in Israel[40,41]. The US study consisted of approximately 2200 children irradiated for tinea capitis between 1940 and 1959, and nearly 1400 matched subjects treated by other means. In Israel, about 10840 were treated with X-rays between 1948 and 1960 for the same condition. The incidence of thyroid cancer was compared to that among an equal number of matched controls and among 5400 untreated siblings. The mean thyroid dose was less than 0.10 Gy in both studies.
No thyroid cancer was observed in the US study and all of the eight thyroid adenomas were found in the irradiated population. In Israel, 29 thyroid cancers occurred among the treated subjects versus eight among controls, and the relative risk in the irradiated group was 5.4 (90% CI 2.7–10.8) compared with the two control groups. The strengths of these two studies are the study design and the long follow-up. The US study, however, consisted of a small series of patients and the Israeli cohort had no controls with tinea capitis and also poor data on possible previous radiotherapy of the cases prior to treatment in Israel.

Rochester thymus irradiation study
Approximately 2650 children who were irradiated between 1926 and 1957 for alleged thymic enlargement and 4800 sibling controls were followed up[42–44]. The children were generally less than one year of age at the time of treatment. The thyroid dose ranged from 0.50 Gy to above 10 Gy, and 62% of the irradiated children received less than 0.50 Gy. A total of 30 thyroid cancers and 59 benign tumors have so far been identified in the irradiated group versus one cancer and eight adenomas in the control group. The relative risks for cancer and adenoma increased with the radiation dose to the thyroid (Table 3).

Other studies on children treated with X-rays
Maxon et al.[45] studied 2230 children treated for benign conditions and 960 matched patients with the same diseases who did not receive radiotherapy. In the irradiated group, 16 thyroid cancers and 15 benign tumors were observed, compared with one cancer and two adenomas among the controls.
Schneider et al.[46–48] followed up nearly 5400 subjects given X-ray therapy in childhood for benign conditions between 1939 and 1962. The mean thyroid dose was 7.80 Gy. Of the 2958 patients who were examined or who completed a questionnaire (55% of the cohort), 297 had a thyroid cancer and 551 had benign thyroid nodules. This study had a low follow-up rate, and lacked controls that were subjected to a similar screening procedure. This may have introduced biases that could affect the interpretation of the results.
In Sweden, the cancer incidence was studied in 18030 patients (33% males and 67% females) with skin hemangioma admitted to the Karolinska Hospital between 1920 and 1959[49]. Radium-226 sources were used in 12821 patients, X-ray therapy (mainly < 60 kV) in 2515 patients, and 2694 patients did not receive any radiotherapy. The median age at the time of treatment was six months. The cohort was matched with the Swedish Cancer Register for the period 1958–1982. In patients treated with radium-226 or orthovoltage X-rays (mean thyroid dose 0.3 Gy), 13 thyroid cancers were observed and the relative risk (RR) was 1.85 (95% CI 0.99–3.17). One thyroid cancer was observed among patients given contact X-ray therapy (mean thyroid dose 0.1 Gy) and RR was 1.33 (95% CI 0.03–7.43), and no case occurred in patients who did not receive radiotherapy. In patients treated with ^{226}Ra or orthovoltage X-rays, the risk was higher among those receiving two or more treatments (RR = 3.47; 95% CI 1.39–7.14; n = 7) than for those receiving one treatment only (RR = 1.28; 95% CI 0.47–2.80; n = 6). RR was 2.27 for males and 1.79 for females, but none of the RRs differed significantly from unity. In a case-control study of all 14 thyroid cancers and 53 matched controls from the cohort, the odds ratio (OR) was 1.0 at thyroid doses below 0.1 Gy, 4.8 (95% CI 1.2–19.1) at doses between 0.1 and 0.4 Gy, and 4.3 (95% CI 1.0–19.1) at doses of 0.5 Gy or more[50]. The strengths of this study are the long and complete follow-up, and the use of untreated children with hemangioma as controls. However, no incidence data were available

before 1958, and the study did not have measurements of individual organ doses.

Patients given radiotherapy for cancer

Studies of populations medically exposed to radiation at moderate to high doses can contribute important information on radiation risks in humans. Such populations usually have good dosimetry data and careful follow-up of the individuals, and often also contain non-exposed groups for comparison purpose. Among the disadvantages are the potential effect of the disease for which the patients have been irradiated on cancer risks, and the partial-body nature of the radiation exposure[51].

Childhood is a period characterized by actively growing tissues, which is something that may have an impact on the susceptibility to radiation-induced cancer. In a study from the United States of more than 9000 children with pediatric cancer, a RR of 53 (95% CI 34–80; n = 23) was observed for thyroid cancer occurring after treatment for the first cancer[52]. Following treatment for Wilms' tumor, RR for thyroid cancer was 136 (95% CI 36–347; n = 4), after Hodgkin's disease RR < 68 (95% CI 22–159; n = 5), and after treatment for neuroblastoma 44 = 349 (95% CI 140–720; n = 7).

Similar results were observed in a British study of more than 10 000 three-year survivors of childhood cancer[53]. Three thyroid cancers occurred and RR was 14.1 (95% CI 2.9–41.2). When retinoblastoma patients were excluded RR was 16. RR for thyroid cancer following treatment for CNS tumors was 48.7 (95% CI 10.0–142.2).

The evidence from children irradiated because of a primary cancer shows a high susceptibility to second cancers. These populations contain a relatively high proportion of children who are genetically susceptible to cancer and therefore may be different from other children. The results from exposure following childhood cancers can therefore not be used for estimating risks in the general population.

The thyroid cancer risk was estimated in patients treated for cancer of the cervix[54]. A cohort of approximately 150 000 women with cervical cancer was available from a large number of oncology centers and cancer registries in 14 countries. From this cohort nearly 4200 cases and about matched 6900 controls were selected for a case-control study. The average thyroid dose was estimated at 0.11 Gy and RR (matched) was 2.35 (90% CI 0.6–8.7). The risk increased with increasing dose for women exposed to more than 0.15 Gy (RR = 3.4). The risk was not, however, elevated for patients who were over the age of 60 at the time of treatment. Risk estimates from this series were 123% increase in RR per Gy and an absolute risk of 7.6×10^{-4} PY Gy^{-1}. This study has a good and long follow-up and consists of a large number of patients. Its weakness lies in the potential misclassification of metastatic cancers as new primary tumors and the possibility that patients with cervical cancer may well differ in several aspects from the general population.

Patients exposed to therapeutic or diagnostic ^{131}I doses

With the recognition of the existence of large amounts of this radionuclide and its distribution over large areas, the possible carcinogenic effects of ^{131}I in human beings has become a topic of wide public and scientific interest. The common use of ^{131}I in the diagnosis and treatment of thyroid diseases has also alerted physicians and the general public to possible complications following its use. Data on human exposure to ^{131}I or to any other radioiodine nuclide are scarce. The Marshall Islanders were exposed not only to ^{131}I from fallout but also to external beta and gamma radiation. The greatest part of the radioiodine dose to the thyroid glands emanated from the shortlived radionuclides ^{132}I, ^{131}I and ^{135}I absorbed by inhalation or by ingestion. The higher energy and higher dose rates of these radioiodines could explain the high incidence of thyroid neoplasia in the Marshall Islanders, with risk figures similar to those obtained with external gamma- or X-radiation.

Four radionuclides of iodine are at present available for diagnostic purposes and for therapy of thyroid diseases and are therefore of interest when discussing thyroid radiation carcinogenesis. In this context, ^{99m}Tc-pertechnetate is also of interest (Table 4).

Iodine-131 therapy for hyperthyroidism in the US

In the US, records of about 30 600 patients treated for hyperthyroidism at 25 different clinics were studied[55, 56]. Sixty-three percent of the patients were treated with ^{131}I and 37% with surgery or antithyroid drugs. The median age at treatment was 47 years and only 2% were less than 20 years of age. In the ^{131}I treated group, 19 thyroid cancers (0.1%) and 44 adenomas (0.2%) were observed, in com-

Tab. 4. Half-life and estimated radiation dose to the thyroid gland per µCi administered from various radioiodines and ^{99m}Tc.

Nuclide	$T_{\frac{1}{2}}$	Estimated dose in mrad per µCi administered *
^{123}I (iodide)	13.3 hours	16
^{125}I (iodide)	60 days	820
^{131}I (iodide)	8 days	1300
^{132}I (iodide)	2.3 hours	50
^{99m}Tc (pertechnetate)	6 hours	0.1

* From radiation doses from radioactive substances in medical use. National Institute of Radiation Protection, Sweden, 1969.

parison with eight cancers (0.1 %) and 26 adenomas (0.2 %) among subjects treated with surgery or drugs. The risk for thyroid cancer after ^{131}I therapy was not significantly higher than following other treatment modalities. Hoffman [57] reported a longer follow-up (median 15 years) of about 1000 women treated at the Mayo Clinic. Three thyroid cancers appeared in the ^{131}I treated group and one in the surgically treated group. The standardized incidence ratio based on general population rates was 3.8 ($p = ns$) and the adjusted RR using data from the surgically-treated group was 9.1 ($p < 0.05$). There is a likelihood that this increased risk reflects an artifact; patients in the surgery group may have been at low risk of thyroid cancer because of treatment selection practices, i.e. patients with suspicious nodules were selected for surgery to rule out malignancy [57]. These patients had little thyroid tissue remaining at risk for thyroid cancer since 80–90 % of the thyroid gland had been surgically removed.

In Sweden, more than 4500 patients (mean age 56 years) received ^{131}I therapy for hyperthyroidism at Radiumhemmet, Stockholm [58]. The thyroid doses were estimated at 60–80 Gy per treatment. Fifty-six percent of the patients had one treatment and 44 % two or more treatments. A total of four thyroid cancers were observed versus 3.8 expected on the basis of general population rates. This study has since been expanded and now comprises more than 10 500 patients treated with ^{131}I at seven different oncology departments in Sweden between 1951 and 1975 [59]. Patients were followed for an average of 15 years. Record-linkage with the Swedish Cancer Register identified 18 thyroid cancers (RR = 1.29, 95 % CI 0.76–2.03) more than one year after treatment. The RR for thyroid cancer among patients with Graves' disease was 0.81 and among patients with toxic nodular goiter 1.74, although none of the RRs differed significantly from unity. RR after 10 years was 1.32 (95 % CI 0.61–2.50).

The lack of increased thyroid cancer risk following ^{131}I therapy for hyperthyroidism is likely to be due to the cell killing or sterilizing effects of the high radiation doses from ^{131}I. In addition, the mean follow-up periods were short in both studies, and nearly 1300 surgically treated patients in the US cohort were later given ^{131}I. A weakness of the Swedish study is the lack of controls with hyperthyroidism who were not given ^{131}I therapy.

Diagnostic doses of ^{131}I

The effects of diagnostic doses of ^{131}I was studied in 35074 patients examined for suspected thyroid disorders between 1951 and 1969 in Sweden and followed for an average of 20 years [60, 61]. The mean age at the time of examination was 44 years. The average ^{131}I activity administered to the patients was 2 Bq and the radiation dose to the thyroid gland was approximately 0.5 Gy. Record-linkage with the Swedish Cancer Register for the period 1958–1984 identified 50 cases of thyroid cancer occurring five or more years after the initial ^{131}I examination, and the relative risk was 1.18 (95 % CI 0.88–1.56) after adjustment for region of residence. Patients anticipated to have the highest risk of radiation-induced thyroid cancer, i.e. women and those observed for 10 years or more, showed no evidence of an excess of a dose-response. The Swedish data suggest that ^{131}I might be four times less efficient in inducing thyroid cancer than high dose-rate exposures. In that study, however, 95 % of the exposed individuals were 20 years or older (mean age 45 years). The strength of this study is the long and complete follow-up and the information about the individual administered activities. However, it lacks controls examined for a suspicion of thyroid disorder but not given diagnostic ^{131}I doses.

Dose-response and the risk after low doses

Despite the numerous studies in the area of radiogenic thyroid cancer, important questions remain as to the dose-response pattern and the risk of thyroid tumors following exposure to low doses of radiation. A linear curve provides a reasonable fit to the data of Schneider et al. [47], of the Rochester series [44], and of the Japanese cohort in Hiroshima and Nagasaki [29, 30]. However, the data in these epidemiological studies are not sufficiently strong to preclude the possibility of a linear-quadratic curve, whereas a pure quadratic curve seems highly improbable [62]. Table 5 summarizes some of the findings in the cohorts discussed previously.

The Israeli study on irradiated children observed an increased risk for thyroid cancer after thyroid doses of less than 0.1 Gy [40, 41]. Dosimetric measurements [63–66] have demonstrated that head size, placement of the ports, shield slipping during treatment, and the child moving during therapy could all have affected the magnitude of the radiation dose. The impact of these parameters is difficult to assess. An unknown proportion of the Israeli children could have received total thyroid doses that were higher than that estimated in the study because documentation concerning possible radiotherapy prior to the treatment in Israel was poor.

Shore et al. [44] did not observe any increased risk for thyroid cancer in their tinea capitis series. This cohort contained 87 % males and several studies have shown females to have a higher risk for radiogenic thyroid cancer. The New York cohort was also smaller, and only a total of 1.2 thyroid cancers were expected, which was compatible with the zero observed [62].

The risk for radiogenic thyroid cancer begins between five and 10 years after exposure and the risk is

Tab. 5. Types of epidemiologic studies on radiation-induced thyroid cancer, number of exposed subjects, number of thyroid cancers, and thyroid cancer risk.

Type of study (exposure)	Series	No. of exposed	No. of cancers (exposed)	RR (90% CI)[a] (95% CI)[b]	Excess cancers 10^{-4} PY Gy^{-1}	Reference
Nuclear explosion/ fallout (mixed)	Nagasaki	14242	37	3.23* (2.02–5.03)[a]	1.3	29
	Marshall Islands	250	7	Not given	1.5	31, 33
	Utah, Nevada	1378	0	0	–	34, 35
Radiotherapy for benign (X-rays or gamma rays)	Tinea capitis, Israel	10842	29	5.4	8.3	40, 41
	Tinea capitis, NY	2215	0	0	–	38, 39
	Thymus, Rochester	2652	30	45	3.5	42, 44
	Maxon et al.	1266	16	–	1.5	45
	Schneider et al.	2578	181	–	3.6**	46, 47
	Hemangioma, Sweden	12821	13	1.85 (0.99–3.17)[b]	0.6	49
Radiotherapy for cancer (X-rays or gamma rays)	Cervical cancer	4173	43	2.35 (0.6–8.7)[a]	7.6	54
	Pediatric cancer, US	9000	23	53 (34–80)[b]	–	52
	Pediatric cancer, UK	10106	3	14.1 (2.9–41.2)[b]	–	53
Radioiodine (^{131}I)	Hyperthyroidism, US	19186	19	3.8 (0.7–11.0)[b]	0.06***	55, 56
	Hyperthyroidism, Sweden	10552	18	1.29 (0.76–2.03)[b]	< 0.01	59
	Diagnostic examinations, Sweden	35074	50	1.18 (0.88–1.56)[b]	0.3	60, 61

* 1.00 + versus 0 Gy; ** Shore et al.[62] *** NCRP Report No. 55 [69].

not fully expressed until 10 years or more after irradiation. The excess risk appears to continue unabated up to at least 30–40 years post-irradiation[62, 67].

Host susceptibility factors

The higher risk for radiogenic thyroid cancer among females is a consonant finding in many studies. Females also have a higher natural incidence of thyroid cancer, and the radiation effect may thus be a reflection of the natural incidence, i.e. the relative risk model seems to be more appropriate than the absolute risk model[62, 67].

Many studies have dealt with children who are within a limited range of age at the time of treatment. In the Israeli study, the thyroid cancer risk appeared to be greater among children irradiated at an age less than six years than for those six years or older[41]. Also in the Nagasaki population the risk was higher in subjects 19 years and younger than for those older than 19[29]. The Swedish diagnostic ^{131}I study consisted of adult patients given diagnostic doses, and this could have contributed to the lack of an increased thyroid cancer risk[60, 61].

Jewish ethnicity was suggested in the Rochester series by Hempelmann et al.[43] as another host susceptibility factor, and Shore et al.[62] later confirmed this observation. In the Israeli cohort, thyroid cancer risk also differed among different Jewish ethnic subgroups. Persons born in Israel had one-third the risk of those born in Asia and North Africa (excess risk, 3.4 and 10.2, respectively). The westernized life-style in Israel may be a reason why the excess risk of subjects born in Israel was closer to that of the Rochester cohort[67].

Thyroid suppression therapy has been shown to reduce the number of radiation-induced neoplasms in rats. The apparent reduction of thyroid nodularity among Marshall islanders given thyroid hormones, however, supports the assumption that thyroid suppression also reduces the risk for radiogenic cancer in humans[20]. In a prospective randomized study of 431 patients with radiation-related thyroid nodules, Razack et al.[68] demonstrated that thyroid hormone therapy resulted in complete regression of nodules in 44% of the patients.

Summary

Thyroid cancer is a well documented late effect of exposure to ionizing radiation. The excess risk begins 5–10 years after exposure and continues until at least 40 years after exposure. Females are roughly three times more susceptible to both radiogenic thyroid cancer and to thyroid cancer of other origins than are males. Therefore, relative risk estimates for radiogenic thyroid cancer do not necessarily differ by sex. The excess risk is higher among children exposed prior to five years of age than in those exposed later. The risk for radiogenic cancer following exposure to ^{131}I appears to be lower than that following exposure to high dose-rate external irradiation, and in the Swedish diagnostic study ^{131}I was nearly one fourth as effecient as external X-rays in inducing thyroid cancer. The Swedish data suggest that ^{131}I is substantially less efficient in inducing thyroid cancer than high dose-rate exposures. In that study, however, 95% of the exposed individuals were 20 years or older (mean age 45 years).

Résumé

Cancer thyroïdien dû aux radiations

Le cancer de la thyroïde est un effet tardif bien connu de l'exposition aux radiations ionisantes. L'excès de risque commence 5 à 10 ans après l'exposition et dure au moins 40 ans après l'exposition. Les femmes sont trois fois plus sensibles que les hommes au cancer de la thyroïde provoqué par la radiation, mais aussi aux cancers thyroïdiens d'autres origines; c'est pourquoi les risques relatifs des cancers thyroïdiens radiogéniques ne diffèrent pas selon le sexe. L'excès de risque est plus grand chez les enfants exposés avant l'âge de 5 ans. Le risque d'un cancer radiogénique suite à l'exposition au iode 131 est plus faible que le risque associé à une irradiation externe à haute dose. Une étude suédoise a montré que le pouvoir cancérigène du iode 131 était d'environ un quart par rapport aux rayons X externes. Dans cette étude, cependant, 95% des individus exposés étaient âgés de plus de 20 ans (âge moyen 45 ans).

Zusammenfassung

Schilddrüsenkrebs infolge ionisierender Strahlung

Dass ionisierende Strahlung als Spätfolge Schilddrüsenkrebs induzieren kann, ist epidemiologisch wohl belegt. Das Risiko steigt 5–10 Jahre nach der Strahlenexposition an und bleibt mindestens 40 Jahre nach der Exposition erhöht. Das absolute Risiko ist für Frauen etwa dreimal so hoch als beim Mann. Dies gilt sowohl für die strahleninduzierten als auch die übrigen Schilddrüsenkrebse, so dass das relative Krebsrisiko durch Strahlung bei beiden Geschlechtern etwa gleich hoch ausfällt. Das strahlenbedingte Zusatzrisiko ist höher, wenn die Bestrahlung vor dem fünften Lebensjahr erfolgt ist. ^{131}I scheint ein deutlich geringeres Krebsrisiko mit sich zu bringen als externe Strahlenbelastung mit hohen Dosisraten; in der schwedischen Studie an Patienten, bei denen ^{131}I zur Schilddrüsendiagnostik gegeben worden war, fiel die strahlenassoziierte Krebserhöhung etwa viermal schwächer aus als nach entsprechenden Dosen externer Röntgenbestrahlung (wobei allerdings – bei einem Durchschnittsalter von 45 – nur 5% der diagnostisch Exponierten jünger als 20 Jahre alt waren).

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