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ORIGINAL ARTICLE

Thyroid cancer after exposure to radioactive ^{131}I

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Abstract
The thyroid gland is susceptible to radiation carcinogenesis, and the thyroid cancer risk decreases with increasing age at exposure, with a low risk above 20 years of age at exposure. The risk is best described be a linear dose-response relationship down to 0.1 Gy. Epidemiological studies of patients have not observed any increased risk for thyroid cancer after ^{131}I exposure, but the statistical power to detect risks in children is limited. The Chernobyl accident led to substantial ^{131}I exposure in Belarus, the Russian Federation and Ukraine. About 4 000 cases of thyroid cancer have been diagnosed among those who were children and adolescents in 1986, including about 3 000 in the age group 0–14 years. The risk per Gy from ^{131}I in young subjects may be less than that seen after external low-LET radiation. A recent case-control study found a threefold risk for thyroid cancer among children from severely iodine-deficient areas, as compared with those living in lesser iodine-deficient areas. A threefold risk reduction was observed among those children receiving stable iodine compared with those not receiving iodine.

Ionising radiation is still the only established etiologic factor for thyroid cancer in humans, and the thyroid gland is one of the organs most susceptible to the carcinogenic effect of radiation. A large number of epidemiologic studies have contributed knowledge on radiation-induced thyroid cancer [1]. Age at exposure is an important modifier of risk, and the risk decreases with increasing age at exposure. A linear model best describes the dose-response relationship down to 0.1 Gy, and fractionated exposures may carry a slightly lower risk than acute exposures [2]. For exposures after the age of 20 years, the risk is low for both external radiation and ^{131}I. For those exposed in childhood, elevated risks persist 40 years and more after exposure.

Radioiodines have been used in medicine for more than 60 years. Epidemiologic studies have not, until recently, provided convincing evidence of an increased thyroid cancer risk after ^{131}I exposure, but they all have limited statistical power to detect risks in children [1]. An analysis by Shore [3] written before there were analytic data from the Chernobyl accident, suggested a lower effect of ^{131}I than that seen after exposure to external low-LET radiation, primarily due to the differences in dose-rates. This paper discusses thyroid cancer risk after exposure to ^{131}I.

Thyroid cancer after low doses of ^{131}I

In Sweden, we have followed a large cohort of mostly adults examined with diagnostic ^{131}I during the period 1952–1969 [4–6]. In the follow-up until 1998, Dickman et al. [6] observed 129 thyroid cancers among 36 792 patients. Excess thyroid cancers were observed among the 1 767 patients who reported previous external radiation therapy to the head and neck, with a standardised incidence ratio (SIR) of 9.8 [95% confidence interval (CI) = 6.3–14.6]. Among patients without previous external radiation exposure, SIR = 3.5 (95% CI 2.7–4.4) for 11 015 patients originally referred due to suspicion of a thyroid tumour, and SIR = 0.91 (95% CI 0.64–1.26) for the 24 010 patients who were referred for a reason other than suspicion of a thyroid tumour. The latter group received a thyroid dose of 0.94 Gy. There was no evidence that diagnostic ^{131}I exposure increases risk of thyroid cancer. The study included few patients under age 20, so the results apply primarily to exposure of adults.

Hall et al. [7] studied palpable thyroid nodules in 1 005 women of the same cohort and in 248 controls. The mean thyroid dose was 0.5 Gy, the average age at exposure was 26 years and 52 years at the clinical follow-up. Only 17% were less than 20

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years old at the time of exposure. The prevalence of thyroid nodules was 11% in exposed women and 12% among the controls, with a relative risk (RR) of 0.9 (95% CI 0.6–1.4). When the analysis was restricted to exposed women, the prevalence of nodules was positively associated with thyroid dose, with an excess relative risk (ERR) of 0.9 per Gy (95% CI 0.2–1.9), due to the association for single nodules. ERR was similar for women exposed before and after age 20 years.

In the United States, Hamilton et al. [8] studied 3 503 children who received diagnostic ^{131}I (median dose, 0.4 Gy) and 2 594 controls. Four thyroid cancers occurred in the ^{131}I-exposed group and one cancer among controls (RR = 2.9; 95% CI 0.3–70). Based on population-based thyroid cancer incidence rates, four thyroid cancers would have been expected (SIR = 1.1; 95% CI 0.3–2.8).

Hahn et al. [9] studied 2 262 German patients who had diagnostic ^{131}I (median thyroid dose, 1.0 Gy) and 2 711 patients who had a non-radiological thyroid procedure under the age of 18 years. Follow-up examinations were conducted after a mean period of 20 years in 35% of the exposed and in 41% of the non-exposed subjects. Two thyroid cancers were found in the exposed group versus three in the non-exposed group (RR = 0.86; 95%-CI: 0.14–5.13).

Some 2.7×10^{16} Bq (740 kCi) of ^{131}I were released to the atmosphere from the Hanford Nuclear Site 1944 – 1957. Recently, Kopecky et al. studied thyroid cancer risk among 3 440 children exposed to ^{131}I from the Hanford nuclear site in the 1940s–1950s [10]. The cohort included a sample of all births 1940–1946 in eastern Washington State, and the follow-up occurred until the time of the thyroid examination (1992–1997). Of 5 199 individuals identified, 4 350 were located alive and 3 440 were evaluable (sufficient data for dose estimation and received an examination). Thyroid doses from ^{131}I estimated from interview data. A total of 19 thyroid cancers were observed after thyroid doses of about 0.17 Gy with a maximum dose of more than 1 Gy. There was no evidence of a relationship between ^{131}I and thyroid cancer, benign nodules, autoimmune thyroiditis or hypothyroidism.

Patients treated for hyperthyroidism

Iodine-131 is used to treat hyperthyroidism with the aim to deliver a thyroid dose of 60–120 Gy. In the United States, a total of 35 593 hyperthyroid patients were treated 1946–1964 in the original Cooperative Thyrotoxicosis Therapy Follow-up Study, and 65% were treated with ^{131}I [11]. By the end of follow-up in December 1990, 49% were still alive. Radioactive iodine was not linked to total cancer deaths or to any specific cancer with the exception of thyroid cancer, for which a standardized cancer mortality ratio (SMR) of 3.94 (95% CI, 2.52–5.86) was found. The authors concluded that while there was an elevated SMR following ^{131}I treatment, in absolute terms the excess number of deaths was small, and the underlying thyroid disease appeared to play a role.

We have studied cancer incidence and mortality in about 10 500 Swedish patients receiving ^{131}I in 1950–1975 [12,13]. Follow-up was on average 15 years and the mean total activity was about 500 MBq. Average doses to organs other than the thyroid were relatively low, with the highest doses to the stomach (0.25 Gy). SIR for thyroid cancers was 1.3 (95% CI 0.8–2.0; n = 18) and did not differ for the 10-year survivors. SMR for thyroid cancer was 1.95 (95% CI, 1.01–3.41, n = 12), but this was due to a high risk shortly after therapy, and SMR more than 10 years after therapy was 0.66 (95% CI 0.08–2.37).

Franklyn et al. [14] conducted a population-based study in 7 417 UK patients treated between 1950 and 1991. There were significant increases in incidence and mortality for thyroid cancer (SIR = 3.25; 95% CI 1.69–6.25 and SMR = 2.78; 95% CI 1.16–6.67), although the absolute risk was small.

Thyroid cancer after the Chernobyl accident

The Chernobyl accident led to substantial thyroid doses from ^{131}I and other shorter-lived radioiodines in many areas of Belarus, the Russian Federation and Ukraine. There has been a remarkable increase in thyroid cancer incidence in these regions with more than 4 000 cancers occurring in those exposed under the age of 20 years, starting 4–5 years after the accident and still continuing. The increase is much smaller, or non-existent, in those exposed at older ages.

Since the UNSCEAR 2000 Report [1] several ecological studies have reported statistically significant increase in thyroid cancer among exposed children [15–21]. Jacob et al. [18] estimated the excess absolute risk (EAR) to 2.1 (95% CI 1.0- 4.5) per 10^4 PYGy for settlements in Belarus and the Russian oblast Bryansk. This is about half of that seen in subjects less than 20 years exposed to external radiation. ERR was 23 (95% CI 8.6–82) per Gy and higher than the corresponding estimate for external radiation, but there is uncertainty in background rates. Shakhtarin et al. [19] found that risks in Bryansk were twice as great in areas with iodine deficiency as in those with adequate iodine status. Ivanov et al. [20] observed an ERR for Bryansk of 11.9 (95% CI 7.2–16.6). Likhtarov et al. [21] observed a strong dose-response relationship in children in the most heavily contaminated Ukrainian

oblasts, with ERR = 11.89 (95% CI 6.54–23.96) and EAR = 1.55 (95% CI 1.22–1.90) per 10^4 PY Gy.

A few analytic studies of thyroid cancer have also been reported [22–25]. Astakhova et al [22] conducted a case-control study of 107 children with thyroid cancer from Belarus. The odds ratio (OR) was 5.4 (95% CI 1.5–16.7) for the group receiving 1 Gy or more compared to those receiving <0.3 Gy. Davis et al. [23] studied 26 cases from the Bryansk oblast and two controls per case. The thyroid cancer risk increased with dose: ERR = 1.65 per Gy (95% CI 0.10–3.20).

The largest population-based case-control study to date was carried out by Cardis et al. in Belarus and the Russian Federation, including 276 cases less than 15 years at exposure and 1 300 matched control subjects (24). Individual thyroid doses were estimated and the subjects' iodine status at the time of the accident was estimated. A linear dose-response relationship was observed up to 1.5–2 Gy ($p < 0.001$), whereas a linear-quadratic curve provided the best fit for the full range of exposure. OR at 1 Gy varied from 5.5 (95% CI 3.1–9.5) to 8.4 (95% CI 4.1–17.3) depending on the risk model. The radiation-related risk of thyroid cancer did not differ significantly between males and females or by time since the accident. RR was 3.2 (95% CI 1.9–5.5) in iodine-deficient areas as compared to elsewhere. Most of the areas studied are deficient in soil iodine, and so the comparison group is not really iodine sufficient. Administration of potassium iodide as a dietary supplement reduced the risk of thyroid cancer by a factor of 3 (RR = 0.34, 95% CI 0.1–0.9). The authors concluded that both iodine deficiency and iodine supplementation appear to modify the risk for radiation-induced thyroid cancer.

There are several ecological studies on recovery operation workers and there is little, if any, evidence of an increased thyroid cancer risk in those exposed as adults [26–29]. Some reported increases could be explained by a screening effect among the exposed groups.

Discussion

More than half a century of studies of radiation-induced thyroid disease shows that age at exposure has a strong influence on risk, and may be more influential than dose. In fact, the radiation risk appears minimal after exposure in adulthood [1]. A linear dose-response fits the data on radiation-induced thyroid cancer following exposures in childhood. The ERR per Gy for childhood exposures is higher than the risk coefficient reported for any other solid tumors.

Exposure to ^{131}I from medical procedures have not demonstrated convincing evidence of an increased thyroid cancer risk, but this can be due to their limited power to detect risks in children [1]. Shore suggested that any effect of ^{131}I is lower than that seen after exposure to external low-LET radiation, primarily due to the differences in dose-rates [3].

The Chernobyl accident has focused the attention on the etiologic role of ^{131}I for thyroid cancer. There is clearly a causal relationship between exposure to radioactive iodines from the accident and the remarkable increase in thyroid cancer incidence among those exposed as children or young people in Belarus, the Russian Federation and Ukraine. More than fifteen years after the Chernobyl accident, thyroid cancer incidence is still high. The same is not clear for those exposed as adults, and reported increases might be accounted for by increased screening of the population.

A great deal has been learnt from the Chernobyl accident. There is an increased risk of thyroid cancer, especially in those who were children or adolescents at the time of the accident and in those with the highest thyroid doses from radioiodine. Absolute risk estimates based on ecological studies suggest that that the risk per Gy in subjects less than 20 years may be about half of that seen after external low-LET radiation. Analytical studies indicate that the risk per Gy may be slightly less, but similar to and statistically compatible with that seen following external exposures. Radioiodine constitute a significant health hazard to those so exposed, and there is a need to reduce the uncertainties in thyroid dose estimation and the effects of screening in order to better define the dose-response relationship for thyroid cancer.

The magnitude of the effect in those exposed in childhood and adolescence needs to be followed. Iodine deficiency and subsequent dietary supplementation with stable iodine both appear to substantially modify the risk of radiation-induced thyroid cancer in young people. Only two studies to date [19,24] have looked at the influence of iodine deficiency on thyroid cancer risk. Poland can serve as an illustration of the importance of good iodine status to reduce the consequences of exposure to radioiodines. In Poland, the effective administration of stable iodine reduced substantially the thyroid doses from ^{131}I. Further studies are needed to address the role of stable iodine and other possible modifying factors.

It is noteworthy that the risk for thyroid cancer appeared to be concentrated among children living in severely iodine-deficient areas, with a threefold risk compared with those living in lesser iodine-deficient areas. This suggests a role for the promoting effect of iodine deficiency [30]. It is also interesting that stable iodine administered months after the exposure would reduce thyroid cancer risk. A threefold risk reduction was observed among those

children receiving stable iodine as dietary supplement compared with those not receiving iodine.

Future studies of the health consequences of the Chernobyl accident will shed more light on the late effects of ^{131}I exposure. From a scientific point of view, there is a need to evaluate and understand the relationship between exposure and health effects. From a human point of view, there is also an obligation to provide an objective analysis of the health consequences of the accident for the people involved.

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