Relationship between dose and response in thyroid cancer caused by Radiation

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Abstract
The relationship between radiation exposure and the development of thyroid cancer has been well established, and the dose of radiation given to the thyroid gland and the age of exposure are the two main risk factors for the disease. After receiving a mean dose of more than 0.05–0.1 Gy, the risk increases (50–100 mGy). The risk is greater in childhood, diminishes with exposure age, and is minimal in adults. The minimum latency period following exposure is 5–10 years before thyroid cancer manifests. The most common type of thyroid cancer discovered after radiation exposure is papillary carcinoma (PTC), with a higher prevalence of the solid subtype in young children and a short latency period for papillary carcinoma (PTC) in adults. After receiving a dose of radiation to the thyroid greater than 0.05–0.1 Gy, the risk of developing thyroid cancer is greater in childhood and diminishes with age.

Keywords: Differentiated thyroid carcinoma; radiation-induced thyroid cancer; radiation exposure; Chernobyl accident.

Introduction

Ionizing radiation exposure during childhood and adolescence has a strong carcinogenic effect on the thyroid gland, which is extremely sensitive to it. In 1950, following radiation exposure to the thymus shortly after birth, the first link between radiation exposure and thyroid cancer was discovered[1]. The first solid malignant tumor with an increased incidence among Japanese atomic bomb survivors was thyroid carcinoma [2]. As a result of the fallout from the nuclear plant accident in Chernobyl and the thermonuclear explosion in the Marshall Islands, an elevated risk of thyroid cancer was later discovered [3]. Radiation doses of 50 to 100 mGy to the thyroid are associated with a significant increase in risk, and higher doses are associated with an increase in risk[4]. The risk is greatest for those who were exposed at the time of the incident, with a peak for those most heavily exposed to radiation [5]. Following radiation exposure, one-third of thyroid tumors are malignant, and papillary thyroid carcinoma makes up the majority of radiation-induced thyroid cancers (PTC). PTC happens at least five to ten years after radiation exposure and may take place years or decades later[6]. These cancers share clinical characteristics with PTC, which develops at a similar age in people who have not been exposed to radiation and is typically not an aggressive form of cancer [7]. The apparent incidence of radiation-induced thyroid cancer is closely correlated with the types and extent of screening, as has been shown for sporadic thyroid carcinomas[8]. The apparent incidence of thyroid cancer in South Korea, where screening procedures were first implemented in 2000, increased by 15 times in the years that followed. Populations in Belarus after the Chernobyl accident and in Japan after the Fukushima accident have much higher rates of thyroid cancer at ultrasonography screening than at clinical examination [9]. Even though the majority of studies found that people who were exposed to radiation during their childhood

and adolescence had a higher incidence of thyroid cancer, it's important to remember that the methods used to screen for thyroid abnormalities may also have had an impact on how much of an increase there was. While it is true that there has been a clear increase in thyroid cancer cases in the countries mentioned, it is important to remember that the implementation of screening procedures as well as the methods used to screen for thyroid abnormalities may also have had an impact on how much of an increase was seen . Therefore, the Physician Coalition for Prevention of Over diagnosis of Thyroid Cancer put in place an initiative that discourages the use of US screening in order to reduce the incidence of thyroid cancer .[10]

Ionizing radiation-

Ionizing radiation is a type of radiation that has enough energy to ionize atoms and molecules by removing electrons from them, creating charged particles called ions. This type of radiation can be harmful to living organisms because it can damage DNA, which can lead to mutations and cancer**.**

Examples of ionizing radiation include X-rays, gamma rays, and alpha and beta particles. X-rays and gamma rays are forms of electromagnetic radiation, while alpha and beta particles are subatomic particles emitted by certain radioactive materials. Ionizing radiation is used in many medical procedures, including X-rays, CT scans, and radiation therapy for cancer. However, exposure to ionizing radiation can also occur from natural sources, such as cosmic radiation from space and radioactive materials in the earth's crust.

The potential health effects of ionizing radiation depend on the type, dose, and duration of exposure, as well as individual factors such as age and overall health. High doses of ionizing radiation can cause radiation sickness, while prolonged exposure to lower doses can increase the risk of cancer and other health problems.To Minimize the risk of harm from ionizing radiation, it is important to follow appropriate safety procedures and guidelines when using radiation in medical procedures or other settings. This may include wearing protective equipment, limiting exposure time, and monitoring radiation levels.

Data in Epidemiology

External-radiation

Children with benign conditions including thymus enlargement, skin angiomas, adenoids or neck lymph nodes, acne, otitis, or tinea capitis were treated with external radiation from 1920 until the 1950s. Even external radiation therapy for a thoracic or abdominal tumor in young children may deliver significant radiation doses to the thyroid gland due to their small body size. External radiation therapy for malignant diseases of the neck, such as Hodgkin's disease, may deliver high radiation doses to the thyroid gland.

Nuclear exposure

The United States Army Air Forces dropped a fission bomb over Hiroshima, Japan, on August 6, 1945, and another bomb over Nagasaki, Japan, three days later. The Radiation Effects Research Foundation has been examining the long-term effects of radiation exposure on atomic bomb survivors' health since 1950. 371 thyroid tumors were found in the 105,401-person cohort between 1958 and 2005. After receiving 1Gy at age 10, the extra relative risk of developing thyroid cancer was calculated to be 1.28 (95% CI: 0.59-2.70). The danger was negligible for those exposed after the age of 20, and it reduced with increasing age at exposure. Among people exposed to radiation before the age of 20, about 36% of thyroid cancer cases were caused by radiation. 245 people were exposed to internal radionuclides and external beta and gamma radiation in March 1954, following the Bravo nuclear test on the Bikini Island. Short-lived radioactive isotopes of iodine were responsible for about 80% of the thyroid radiation dosage. When cases of hypothyroidism and thyroid nodules were found in exposed people, levothyroxine treatment was started. 34 years after the test explosion, 245 exposed individuals had 55 (22%) thyroid nodules detected, including 16 (7%) thyroid carcinomas. Among 1,495 unexposed participants from the same region, 22 (1.5%) nodules, including 7 (0.5%) carcinomas, were discovered (3, 14). With increasing radiation dosage to the thyroid gland, exposed patients had higher rates of hypothyroidism, thyroid nodules, and thyroid

cancer. The risk of acquiring a thyroid nodule reduced with exposure age and was higher (3.7 fold) in females than in boys. The study was expanded to include participants who resided on atolls far from Bikini Island in 1987, and the results demonstrated that the frequency of thyroid nodules rose with decreasing distances from Bikini Island. A more recent investigation was unable to support or contradict these findings. Longer follow-up really reduces the risk of radiation-induced thyroid cancer, whereas the risk of spontaneous thyroid.

Huge quantities of radiation, including a lot of radioactive iodine, were discharged into the atmosphere in 1986 following the accident at the nuclear power station in Chernobyl, Ukraine. The high level of contamination (no food restrictions, no shielding, and late evacuation of only some contaminated populations) and the high uptake of radioiodine in the thyroid gland (iodine deficiency and no iodine prophylaxis) resulted in a high radiation dose to the thyroid gland in Belarus, Ukraine, and South Russia. Wind in the days following the disaster caused the radioactive cloud to extend over considerable portions of northern and Western Europe. 1990, just 4 years after the catastrophe, saw the discovery of the first thyroid cancer cases in exposed young children.
After that, the prevalence of pediatric thyroid cancer rose, reaching a high of 40 cases per million in Belarus in 1995. The 2 million heavily contaminated people who were under the age of 18 at the time of the disaster are thought to have had 7,000 incidences of thyroid cancer. The radiation dose administered to the thyroid gland and the likelihood of developing thyroid cancer in children were found to be closely related.

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Factors Affecting Sensitivity to Radiation-Related Thyroid Carcinoma Ogenesis-

Radiation dose delivered to the thyroid gland

The radiation dose given to the thyroid gland is the greatest risk factor for the development of thyroid cancer after radiation exposure. The incidence of thyroid cancer dramatically increased after a mean dose to the thyroid during childhood as low as 0.05 to 0.1 Gy, according to a pooled analysis of seven research (5) that was recently expanded to 12 studies .(50 to 100mGy).
Yet, there is no dose below which the risk may be completely eliminated). As a result, irradiating treatments like CT scans, which can give up to 10 mSv of radiation, should be avoided wherever feasible and should only be conducted if absolutely necessary. The risk

increases linearly with dosage up to 20–29 Gy (OR: 9.8, 3.2–34.8), and there is a decline in dose response at doses more than 30 Gy. Although this supports the cell-killing theory, the risk is still high.

The relative risk of thyroid cancer in children exposed to a dosage of 1 Gy to the thyroid varies among series from 5.1 to 8.5. According to estimates, radiation exposure is to blame for 88% of the thyroid malignancies in this group of patients. Children who were exposed to radiation externally and who were living in Belarus and Ukraine at the time of the Chernobyl event showed a similar relative risk.

Due to the observation of radiation-induced thyroid tumors following high dose rates of external radiation in the past, it was previously believed that the dose rate (Gy/time unit) was a crucial factor. However, the study of subjects exposed to 131I for medical reasons in Sweden did not find any evidence of an elevated risk of thyroid cancer. The presence of thyroid cancers in the Marshall Islands has also been linked to exposure to iodine radioisotopes with short half-lives. IIn actuality, Swedish individuals were exposed as adults, when humans are least sensitive to radioiodine's carcinogenic effects (see below). The Chernobyl disaster's effects made it abundantly evident that thyroid tumors can develop in children at low dose rates due to radioactive iodine contamination, especially with 131I, with comparable risk factors as external radiation exposure at high dose rates.

The latency of age

Those who received external radiation before the age of 4 years had a fivefold higher risk per Gy of developing thyroid cancer than those between the ages of 10 and 14 years, according to a pooled analysis of 12 trials. Similarly, a study of thyroid cancer after external radiation therapy for childhood cancer discovered that radiation treatment between the ages of 0 and 1 year was associated with a 10-fold higher excess relative risk per Gy (ERR/Gy) than radiation treatment between the ages of 15-20 years . Similar findings were made for Japanese survivors of atomic bombings and the Chernobyl disaster, for whom the risk was highest when exposure occurred when they were young and dropped as exposure age increased. The incidence of thyroid cancer following external radiation exposure was thought to be 2-3 times higher in women than in men, but this gender impact was not verified in the pooled analysis of 12 research studies and was not discovered in children exposed to radiation after the Chernobyl accident.

The minimum latency period for thyroid cancer development after radiation exposure was 5–10 years. The Chernobyl accident did result in a shorter interval, which may be related to the large number of contaminated children, among whom only a few cases of thyroid cancer had previously occurred. This represents a significantly increased incidence due to the disease's rarity in the general population at that young age (4). Yet, among those who survived the bombings of Nagasaki and Hiroshima, an extra risk is still present 60 years after exposure. The risk rises and peaks at 20–35 years, then declines (5,).

Role of iodine in thyroid cancer

Due to a high thyroid uptake of radioactive iodine in cases of iodine insufficiency, the thyroid gland receives substantial radiation doses. Children exposed to contaminants in Belarus, Ukraine, and Russia may have seen an increase in thyroid cell proliferation due to iodine deficiency, which may help thyroid cancer develop. The incidence of thyroid cancer increased after splenectomy and decreased after high radiation doses to the pituitary gland in a cohort of 4,338 survivors of solid childhood cancer who were followed for five years. The authors postulated that reduced serum TSH levels following pituitary irradiation will result in less thyroid stimulation and that immunological changes following splenectomy may contribute to the development of thyroid cancer. Chemotherapy administration was not previously thought to increase the incidence of thyroid cancer after radiation treatment for pediatric cancer or to potentially alter the radiation dose response (5). However, it is currently believed that chemotherapy during children adds to the risk of radiation therapy when both are administered, increasing the chance of thyroid cancer in the future by 4 times if given alone. In patients with a body mass index (BMI) greater than 25 or a bigger BSA (body surface area), the probability of thyroid cancer per unit of

radiation dosage to the thyroid was higher .These findings indicate that a variety of factors may affect the chance of receiving any radiation dosage to the thyroid gland, although biases in screening should always be taken into consideration.

Molecular biology of papillary thyroid carcinoma and its related pathologies

The most typical type of thyroid cancer discovered after radiation exposure is PTC. During the Chernobyl tragedy, the majority of young children exhibited aggressive behavior and a short latency period for the solid or follicular PTC subtype, whereas older children exhibited less aggressive behaviorand a longer latency period for the classical PTC subtype. In the uncommon PTC that developed in young children without any radiation exposure, the solid subtype was also often seen, indicating that it is linked to a younger age at tumor development Either directly or by producing reactive oxygen species (ROS), ionizing radiation damages DNA. NADPH oxidases, or NOX/DUOX as they are more commonly known, are specialized ROS-producing enzymes that are abundant in thyroid tissue. The thyroid gland's great sensitivity to radiation may be explained by the fact that radiation exposure enhances DUOX1 expression, which causes an important ROS generation in the thyroid gland following radiation exposure. Single-strand or double-strand breaks in the DNA can lead to deletions and chromosomal rearrangements.

When the body is growing, especially before the age of five, normal thyrocytes multiply, which will encourage the accumulation of genetic abnormalities following radiation exposure. Age-related declines in mitotic rate lead to very low levels in adults. This may account for the thyroid gland's high sensitivity to radiation's carcinogenic effects at birth, which declines with age and becomes low or insignificant after the age of 15-20 years (5). Intra-chromosomal rearrangements are typically seen in PTC that develops after radiation exposure. The tyrosine kinase domain of RET is fused with the NH2 terminal domain of another gene that is widely expressed in RET/PTC rearrangements, leading to the constitutive production of the transcript. Early aggressive PTC in children that followed the Chernobyl accident most typically showed RET/PTC3 rearrangement, while later classical PTC that followed the accident was more likely to show RET/PTC1 rearrangement. Additional RET/PTC rearrangements, which may vary depending on the partner gene or the breakpoint site, have been discovered in Chernobyl thyroid tumors. RET/PTC, BRAF, and TRK rearrangements, as well as kinase fusion oncogenes that activate the mitogen-activated kinase pathway (MAP kinase pathway), were discovered in 23 of the 26 papillary thyroid cancers in Ukraine's highly contaminated children, while BRAF (n = 2) and TSHR (n = 1) gene point mutations were only discovered in 3 tumors (6).). In contrast, gene rearrangements were discovered in 9 of the 27 sporadic papillary thyroid cancers that affected uncontaminated Ukrainian infants, BRAF (n = 7) or NRAS (n = 2) gene point mutations were discovered in 9 tumors, and no driver mutation was discovered in 9 tumors. In summary, point mutations are uncommon in radiation-induced PTC but gene rearrangements are often observed. In rare PTCs that develop in children without prior radiation exposure, RET/PTC gene rearrangements are more common than in adults but less frequent than in radiation-induced PTC.

With a sensitivity of 0.92 and a specificity of 0.85, a transcriptomic signature that contains genes that are different expressed in sporadic cancers compared to tumors originating after external radiation exposure during childhood allows the separation of these two groups of tumors. Also, this characteristic enables the classification of cancers from Belarus and Ukraine as either sporadic or developing in people who were exposed to high levels of contamination during the Chernobyl tragedy. These findings support earlier research and imply that radiation-induced cancers might have some unique genetic traits, although this needs to be validated on a larger sample of malignancies.

How to manage the risk of developing PCT

For the long-term monitoring of late effects of radiation to the neck, the risk of developing thyroid cancer and its temporal pattern of incidence are of therapeutic interest. The practitioner may regularly encounter patients who have been exposed to external radiation

or those who have thyroid abnormalities that call for the investigation of a history of radiation exposure. The risk of a thyroid tumor caused by external radiation exposure can be calculated based on the age at exposure and the dose given to the thyroid gland; it's also crucial to check for other radiation side effects and a personal or family history of head and neck malignancies. A thorough physical examination is conducted, and areas surrounding the thyroid gland and lymph nodes are imaged using ultrasound. Moreover, screening should be done for conditions including salivary gland tumors, hyperparathyroidism, and brain tumors that may be brought on by radiation exposure to the neck. Laboratory testing can check for hyperparathyroidism and hypothyroidism (TSH) (calcium). The chance of developing hyperparathyroidism rises with radiation doses when children are exposed to radiation. Thyroid nodules are more likely to form in radiation-exposed individuals with high Tg levels and normal clinical exams. Individuals who have a history of radiation exposure as children should be given a lifetime of follow-up (7-8). According to risk factors, patients without anomalies might undergo evaluations every 1 to 5 years. Fine needle biopsy is performed on solid thyroid nodules greater than 1 cm in diameter for cytology. Nodules that are worrisome at ultrasound are recommended for fine needle biopsy if several nodules are discovered. Ultrasonography is used to manage patients with sub centimeter nodules once every two to three years. Levothyroxine is used to treat hypothyroidism. In order to keep the serum TSH levels in the low normal range, levothyroxine medication is also taken into consideration for thyroid people with high risk factors and for patients with tiny nodules. A complete thyroidectomy is advised if the results of the cytology indicate the presence of a papillary cancer. When surgery is chosen for a nodule that appears to be benign, a total thyroidectomy is also carried out in an effort to lower the likelihood of nodule recurrence.

Thyroid cancer prevention techniques

The evaluation of the Chernobyl accident's effects has amply shown that thyroid cancer risk is increased when children are exposed to radioactive isotopes of iodine. Therefore, it is advised to prevent any thyroid irradiation in the event of atmospheric contamination by using shielding, limiting one's intake of certain foods, and, if necessary, evacuating the area. Large doses of stable iodine should also be administered.

When given several hours before contamination, at the moment of contamination, and six hours after the accident, stable iodine, supplied as potassium iodide (KI), decreases thyroid uptake of radioactive iodine by more than 98%, 90%, and 50%, respectively. 48 to 72 hours of poor uptake will be followed by an increase.

KI prophylaxis should be given to youngsters and expectant women first. For persons over 60 or with heart or circulatory disorders, it is not advised. In patients with thyroid autonomy or nodular goiter, KI can cause thyrotoxicosis (9-10). After the Chernobyl disaster, KI doses were given to nearly 18 million people in Poland, although no cases of thyrotoxicosis have been documented, and only a small number of those people experienced symptoms. There were temporary increases in serum TSH in the infants of mothers who took KI at the end of their pregnancies, and no neurological after effects were noticed. The population in France within ten kilometers of one of the country's 19 nuclear power reactors received KI. The public authorities will determine the need for and timing of iodine prophylaxis in the event of air contamination. Each tablet sold in France has a chemical stability of at least 5 years and includes 65 mg of KI, which is comparable to 50 mg of iodine. The pills can be broken into 4 pieces and dissolved in liquids like water, milk, or fruit juice. Consuming these tablets on an empty stomach is not advised. The dosages that are suggested are: 100 mg of iodine (130 mg KI, two tablets) for adults (including pregnant women); 50 mg of iodine (65 mg KI, one tablet) for kids under 13; 25 mg of iodine (32.5 mg KI, half tablet) for kids under 3; and 12.5 mg of iodine (16 mg KI, quarter tablet) for infants.

The International Atomic Energy Agency considers a dose of at least 50 mSv to be the intervention threshold for administering stable iodine to children's thyroid glands. Western nuclear reactors have filters that will lessen the level of air contamination and an isolating barrier (which was absent from the Chernobyl

plant), which should provide a delay of several hours between a catastrophic accident and the release of radioactive material into the atmosphere. The government must take advantage of this window of opportunity to set up iodine prophylaxis (11-12).

Conclusion

The thyroid gland's exposure to radiation has well-known effects. Younger children at the time of exposure have a higher chance of developing thyroid cancer following exposure to doses greater than 0.05–0.1 Gy. To protect children from radiation exposure during childhood, every effort should be made.

Results

Regarding clinical courses, thyroid cancer is more aggressive in children and teenagers. There are no discernible distinctions between radiation-induced cases and spontaneous instances in terms of their fundamental clinical characteristics. Even the most advanced stages of pediatric thyroid cancer can be successfully treated by utilizing tried-and-true treatment plans that include surgery, radioiodine therapy, and thyroid hormone replacement. Even in situations brought on by radiation, thyroid cancer in children and adolescents has a low mortality rate (1-2%). It must be remembered, nevertheless, that thyroid cancer relapses can occur years or even decades after the initial diagnosis. Because of this and to manage therapy-related problems, thorough follow-up is required for life.

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