Thyroid Cancer in Regions Most Contaminated after the Chernobyl Disaster

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ABSTRACT

Exposure to ionizing radiation, especially during childhood, is a well-established risk factor for thyroid cancer. Following the 1986 Chernobyl nuclear power plant accident the total number of cases of thyroid cancer registered between 1991 and 2015 in males and females who were less than 18 years old exceeded 19,000 (in Belarus and Ukraine, and in the most contaminated oblasts of the Russian Federation). However, as indicated by the United Nations Scientific Committee on the Effects of Atomic Radiation the fraction of the incidence of thyroid cancer attributable to radiation exposure among the non-evacuated residents of the contaminated regions of Belarus, Ukraine and Russia is of the order of 0.25. Apparently, the increased registration of thyroid neoplasms in the parts of these countries is a classical 'screening effect', i.e., massive diagnostic examinations of the risk-aware populations performed with modern eqipment resulting in detection of many occult neoplasms (incidentalomas). Moreover, one type of thyroid cancer previously called 'encapsulated follicular variant of papillary thyroid carcinoma' is non-invasive and instead of 'carcinoma' should now be recognized as 'noninvasive follicular thyroid neoplasm with papillary-like nuclear features.' Other potential causes of overdiagnosing of thyroid tumors include increase of the spontaneous incidence rate of this disease with age, iodine deficiency among children from Belarus, Russia and Ukraine, and/or consumption by these children of drinking water containing high levels of nitrates that likely coincides with the carcinogenic effect of radiation on the thyroid gland.

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Keywords

Chernobyl Accident; Thyroid Cancer; Radiation, Ionizing; Contamination; Incidence; Overdiagnosis

Introduction

At 1:24 a.m. on April 26, 1986, the worst nuclear disaster in history occurred at the Chernobyl Nuclear Power Plant (CNPP): the critical design flaws of the RBMK-type nuclear reactors which were unknown to the operators combined with the general Soviet disregard for safety culture led to explosion of the CNPP's reactor no. 4. The blast, followed by an open-air reactor core fire, over about nine days were releasing considerable amounts of radioactive substances that precipitated mostly onto the nearby areas of the Byelorussian, Ukrainian, and Russian Soviet Socialist Republics, currently known as Belarus, Ukraine and the Russian Federation, respectively; in the most heavily afflicted Byelorussian SSR more than 23% of the area and about 20% of the population were contaminated [1].

One of the major radioactive products of nuclear fission occurring inside nuclear reactors is iodine-131 (^{131}I, half-life 8.02 days). Due to its

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volatility, short half-life, and high abundance in fission products, ^{131}I is responsible for the largest part of radiation exposure during the first week after environmental contamination from the radioactive fallout produced by a seriously damaged nuclear power plant. The high energy beta radiation (up to 606 keV) emitted by ^{131}I makes it the most carcinogenic of the iodine isotopes because the beta radiation from this radionuclide penetrates 0.6-2.0 mm of tissue from the site of uptake, and hence can potentially induce oncogenic mutations in the surrounding thyroid cells.

One of the most sensitive organs for radiation-induced carcinogenesis is the thyroid gland [2,3]. The thyroid gland is unique in the body as it concentrates iodine, in both stable and radioactive forms. As a result, exposure to radioiodine from the Chernobyl fallout posed a particularly increased danger, with the largest radiation doses to inhabitants coming from ingesting (primarily through milk) and inhaling radioactive iodine-131 (^{131}I) [4-6].

According to the estimations performed by the United Nations Scientific Committee Effects of Atomic Radiation (UNSCEAR), the total number of cases of thyroid cancer registered between 1991 and 2015 in males and females, who were less than 18 years old in 1986 (in Belarus and Ukraine and in the four most contaminated areas of the Russian Federation), amounted to 19,233. At the same time, the Committee estimated that “the fraction of the incidence of this cancer attributable to radiation exposure among the non-evacuated residents of these regions who were children or adolescents at the time of the accident is of the order of 0.25 (the uncertainty of the estimated attributable fraction ranged from 0.07 to 0.5)” [7]. Therefore, factors other than radiation exposure may play a more significant role in the rise of post-Chernobyl thyroid cancer.

Thyroid cancer

Thyroid cancer, the most common endocrine malignancy, has significantly increased across many countries over the past few decades [8-12] due to the growing use of highly sensitive imaging techniques to detect many small, non-palpable thyroid nodules, often referred to as incidentaloma [12-15]. The recognized risk factors for thyroid neoplasms include iodine deficiency, congenital goitre, familial incidence of thyroid pathologies, and last but not least, radiation exposure, especially during childhood [3,13,16-21]. The incidence of thyroid nodules increases with age (typically, in 35- to and 65-year-old people), and is more frequent in women [13]; currently, thyroid cancer has likely become the third-most common cancer in females, with an annual incidence of 37 per 100,000 [22]. Detection and diagnosis of thyroid cancer relies on a combination of imaging techniques: ultrasound (sonography), radioactive iodine scans (scintigraphy), and CT scans. Additionally, fine-needle aspiration biopsy of the thyroid gland plays a crucial role in accurate detection and differentiation between benign and malignant thyroid lesions [23].

Thyroid cancer can be categorized into four main types based on their microscopic appearance: papillary (the most common, accounting for 70-85% of cases), follicular (10-20%), medullary (5-10%), and anaplastic (less than 5%). Additionally, there are rare types like Hürthle cell tumor, thyroid lymphoma, and squamous cell carcinoma.

The first two types, papillary and follicular, are classified as Differentiated Thyroid Cancers (DTC) with excellent prognosis. With treatments like total thyroidectomy (surgical removal of the thyroid) and radioiodine ablation, the 10-year disease-free survival rate for DTC is at least 95%. In most patients, DTC remains an indolent (slow-growing) or fully curable disease. Papillary microcarcinoma, a frequently diagnosed subtype, has a particularly low cancer-specific mortality rate, ranging from 0 to 4% [9,24-29].

In the mid-1970s, scientists distinguished a new type of thyroid cancer: the follicular variant, composed of abnormal follicles (structures that produce thyroid hormones) instead of finger-like projections (papillae) typical of papillary thyroid carcinoma. However, the follicular cells exhibit nuclear features characteristic of papillary cancer. There are two main subtypes of the follicular variant: infiltrative (growing into surrounding tissue) and encapsulated (contained within a capsule). Encapsulated Follicular Variant of Papillary Thyroid Carcinoma (EFVPTC), is particularly noteworthy for its highly indolent (slow-growing and noninvasive) behavior. The incidence of EFVPTC has significantly increased over the past three decades, with an estimation of 10% to 20% of all thyroid cancers diagnosed in Europe and North America [30]. In 2012, the U.S. National Cancer Institute convened a conference to evaluate the problem recognized as "overdiagnosis and overtreatment of typically indolent cancers". A recent conference called for a revision in how a specific type of thyroid tumor is named. Doctors attending the conference argued for replacing the term "cancer" with a less alarming designation. Their reasoning stemmed from data on 109 patients with a particular type of tumor, noninvasive EFVPTC.

Based on these data, a group of 24 thyroid pathologists from seven countries proposed a new name: Noninvasive Follicular Thyroid neoplasm with Papillary-like nuclear features (NIFTP), reflecting the fact that NIFTP tumors have a very low risk of spreading or causing other problems [30]. The level of mortality risk in case of persistent or recurrent NIFTP is less than 1%, and further substantiates the elimination of the term 'carcinoma' from the definition of the popular papillary thyroid cancer [14]. However, as indicated by the Endocrine Section of the American Head and Neck Society's statement, total thyroidectomy remains an option for those cases of NIFTP that can be precisely diagnosed only postoperatively [31].

Incidence of thyroid cancer in regions most heavily contaminated after the Chernobyl accident

As evidenced by epidemiological analyses, external exposure to Low-linear Energy Transfer (LET) ionizing radiation, such as X- and γ-rays, especially during childhood and adolescence, can lead to the development of thyroid tumors [17,21]. Likewise, the relatively high doses of radiation (>0.5 Gy) emitted by radioiodine deposited in the thyroid gland can be tumorigenic [20,29,32-34]. This is confirmed by the markedly increased incidence of thyroid tumors detected in young people from contaminated regions as early as four years following the Chernobyl disaster [1,15,35]. In the majority of these neoplasms, early features and clinical course of the disease appeared to be similar to both non-radiogenic pediatric thyroid cancers as well as to thyroid carcinomas induced by external beam irradiation. A ten-year follow-up of thyroid tumors diagnosed after the Chernobyl accident revealed a disease-specific mortality rate of 1% or less [29], showing a very low risk of death from these tumors. No significant genetic differences were found between these tumors and "spontaneous" thyroid cancers. Additionally, the existence of a specific biomarker to identify radiation-induced thyroid tumors remains unconfirmed and requires further investigation [7,36-40]. Noticeably, apart from thyroid tumors, no other radiation-induced cancers, including leukemia – even in the most significantly exposed 'liquidators' can be associated with the Chernobyl accident [41,42].

Analysis of data by UNSCEAR shows that over 19,200 cases of thyroid cancer were registered between 1991 and 2015 among individuals under 18 who were exposed in Belarus, Ukraine, and the Bryansk, Kaluga, Orel, and Tula regions of Russia. Notably, females diagnosed with thyroid cancer were about four times more numerous than males (Table 1) [7].

A detailed analysis of the incidence rates of thyroid 'cancer' followed up to the year 2015

Table 1: Cases of thyroid 'cancer' diagnosed from 1991 to 2015 among inhabitants of Belarus, Russia, and Ukraine, who were under 18 at the time of the disaster (from [7] with permission).

Gender	Belarus	Russian Federation (Bryansk, Kaluga, Orel and Tula oblasts)	Ukraine	Total
Females	4 546	1 504	9 393	15 443
Males	1 360	334	2 096	3 790
Total	5 906	1 838	11 489	19 233

(broken down into five-year periods) among the Belarusian children and adolescents at the time of the Chernobyl catastrophe are presented in Figure 1 [7]. The highest number of cases (Figure 1a) were diagnosed between 1991 and 1995, particularly in children under 10 who had experienced the Chernobyl disaster, showing a potential link between the disaster and these thyroid cancers in young children.

In contrast, in cohorts of the Belarusian youths (aged 10-19 years at diagnosis), the incidence rate of thyroid neoplasms, especially for the females, peaked during the period 1996-2000 and then decreased (Figure 1b).

Figure 1c shows a steady rise in thyroid cancer diagnoses among Belarusian females who were exposed as children and adolescents during the Chernobyl accident. This increase continued until 2015, when it reached its peak. In contrast, while males also experienced an increase in thyroid cancer rates compared to the pre-Chernobyl period, their incidence remained at a much lower and stable level throughout 1991-2015 (Figure 1c).

Factors contributing to the increased rates of the post-Chernobyl thyroid cancer

The 2018 UNSCEAR 'white paper' summarized data on the dose-response relationships for the detected thyroid cancer estimated for the Belarusian, Ukrainian, and Russian cohorts of people, who were children and adolescents at the time of the catastrophe. These

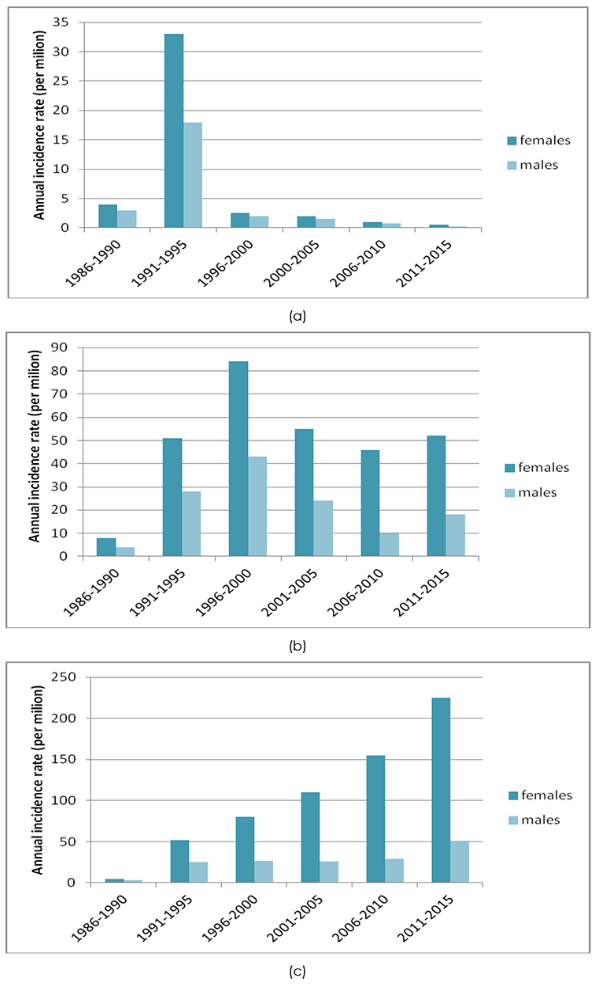

Figure 1: Incidence rates of thyroid 'cancer' among the Belarusian children a) under 10 years old at diagnosis, b) adolescents (age at diagnosis 10-19 years), c) aged under 18 years at the time of the accident (from [7] with permission).

data indicate that the mean doses to the thyroid from the incorporation of ^{131}I were 0.56 Gy for the Belarusians [34], 0.65 Gy for the Ukrainians [33], and about 0.3 Gy and 0.15 Gy for the Russians aged 0-4 years, and 4-9 years, respectively [6]. According to the 2019 WHO data, the mean values of the thyroid dose were 0.54 Gy for the subjects from the Gomel and Mogilev regions of Belarus and 0.10 Gy for the people from the Bryansk, Kaluga, Orel, and Tula oblasts of the Russian Federation [43]. In the Bryansk oblast, the thyroid cancer incidence was 45% and 90% higher in males and females, respectively, than for the whole Russian population. However, when external and internal dose-response analyses were performed, a *negative* rather than a positive association of thyroid cancers with radiation dose was detected [44], showing that the existence of the phenomenon called radiation hormesis, i.e., the *beneficial* rather than the harmful effect of absorption of a low dose of ionizing radiation [45,46]. Consequently, hormesis may help explain why only about a quarter of the detected post-Chernobyl thyroid malignancies can be attributed to the absorption of ^{131}I [7].

A major factor behind the increased detection of thyroid tumors is the significant improvement in diagnosing hidden nodules. These nodules, often called incidentalomas, may never cause symptoms and often go unnoticed throughout a person's life. However, with better diagnostic tools, they are now being identified more frequently during routine autopsies or even by chance during surgeries for unrelated thyroid problems [10,11,47,48]. Indeed, the rate of detection of such nodules has recently significantly increased in developed countries [10-12]. As evidenced by the autopsy studies, occult thyroid nodules occur in 20% to 67% of members of the general public, and modern ultrasonographic diagnostic techniques can detect such nodules in 13% to 50% of living patients [13,22,49]. In different countries, the prevalence of occult thyroid cancers varies from 5.6% in Colombia, 9% in Poland, 13% in the United States, 22% in Spain, 28% in Japan, and 33% in Germany to as high as 35.6% in Finland [8,22,50-53]. A study conducted in the 1980s found that 2.4% of children in Finland had occult thyroid cancers [49]. This is significantly higher than the rates observed in the Bryansk region, where the maximum prevalence was much lower. Similarly, the prevalence of occult thyroid cancers in Minsk, Belarus, during the 1990s was 9.3% [54].

In the aftermath of the Chernobyl disaster, large-scale screening programs for thyroid pathologies were carried out in populations of the contaminated regions of Belarus, Ukraine, and the Russian Federation. The scope, intensity, and precision of the screening were possible due to the use of modern diagnostic equipment and techniques provided by Western countries. According to the government-introduced regulations, all individuals, who in 1986 were below 18 years old and each inhabitant of the contaminated regions of the Byelorussian Soviet Socialist Republic, and later the independent Republic of Belarus, must be diagnosed every year for thyroid malignancy [55]. Execution of the top-down decisions was facilitated by the increased access to health care associated with the enhanced awareness of the risk among the relevant populations. In fact, in accordance with the estimated maximum risk of radiation-induced thyroid cancers to be 15-30 years after the exposure [56-58], the greatest numbers of the post-Chernobyl thyroid malignancies were detected, especially in females, in the period 2011-2015 (Figure 1c).

Increased incidence of thyroid tumors may also be associated with iodine deficiency in the environment [1,18,20]. Low iodine uptake may lead to thyroid hyperplasia and the ensuing higher uptake of iodine. In an irradiated thyroid, in which a malignant transformation has been initiated, iodine deficiency may accelerate the development of a clinical cancer. As indicated by the results of the pilot phase of a countrywide program for the study of goiter prevalence and iodine deficiency in Belarus (established with the assistance of the European World Health Organization [59]) a moderate (at least) goiter endemism and significant iodine deficiency was demonstrated in a cohort of 824 children and adolescents from the contaminated areas. Moreover, results of the epidemiologic studies conducted many years before the Chernobyl disaster showed that childhood goiter was common in the contaminated areas, indicating that the prevalence of iodine deficiency at the time of the catastrophe was close to the present level or even greater [1]. It's important to note that in the most contaminated regions of Belarus and Russia, widespread distribution of stable iodine wasn't initiated until months after the disaster [60]. By this time, radioactive iodine (^{131}I) in the environment posed minimal threat. In contrast, Poland began administering stable iodine prophylaxis within 40 hours of detecting the Chernobyl fallout in Warsaw and eastern regions (around April 28th). This program continued for three days, reaching out to approximately 18.5 million people, including adults [42].

Ecological studies conducted in Belarus after the Chernobyl disaster suggest that high levels of nitrates in drinking water might play a role in amplifying the effects of radiation on thyroid cancer rates in exposed children. Nitrates are environmental contaminants commonly used in fertilizers and food preservation. Over time, they can accumulate in groundwater and surface water, potentially entering the air as well [61]. According to the official statistics, from 1960 to 1990, the average nitrate level in drinking water in the Byelorussian SSR rose sharply from 1.1 to 41.6 mg/L, caused by the enhanced use of nitrate fertilizers in agriculture from 4 to 92 kg/hectare. Among 1044 cases of pediatric radiation-related thyroid cancers detected in Belarus, the cancer incidence significantly correlated with the radiation dose, but the effect of radiation was significantly (P=0.004) influenced by the level of nitrates in local drinking water [62].

Conclusion

Following the Chernobyl nuclear power plant explosion in April 1986, doctors began detecting thyroid cancer in people, who were under 18 at the time. Within four to five years, these cases started to emerge. By the end of 2015, the total number exceeded 19,200.

A known risk factor for thyroid cancer is exposure to radioactive iodine, which was significantly released during the Chernobyl disaster. Since children's bodies are more susceptible, it was expected that some would develop thyroid cancer. However, the large number of the cases detected was surprising.

Analysis of the significant increase in the post-Chernobyl thyroid cancer diagnoses reveals several key points: 1) multiple contributing factors: radiation exposure likely explains only a portion (around 25%) of the diagnosed cancers. Other factors like childhood iodine deficiency, high nitrate intake in contaminated areas, and the naturally increasing incidence with age might also play a role, 2) efficacious detection: widespread modern screening and awareness among the affected population have led to the diagnosis of many dormant thyroid nodules (incidentalomas) that wouldn't have been detected otherwise. These nodules often don't cause any symptoms, and 3) revised classification: the encapsulated variant of papillary thyroid carcinoma, with its slow-growing nature, might not be a true cancer. Experts propose renaming it "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" and avoiding unnecessary invasive treatments. This reclassification might explain the very low mortality rate (less than 0.5%) observed in post-Chernobyl thyroid cancer patients, as reported by UNSCEAR until 2011 (with only 15 deaths). Therefore, the majority of thyroid 'cancers' diagnosed in inhabitants of the parts of Belarus, Ukraine, and Russia that were most seriously contaminated in the wake of the Chernobyl catastrophe are not radiogenic and either being asymptomatic nodules detected during massive screening campaigns or are malignant tumors caused by factors not associated with the action of ionizing radiation.

Authors' Contribution

M.K. Janiak conducted conceptualization, investigation, data acquisition and analysis, writing – original draft preparation, writing – review, and editing. G. Kamiński also did investigation, data acquisition and analysis, writing – review, and editing. All the authors read, modified, and approved the final version of the manuscript.

Conflict of Interest

None

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