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Thyroid Cancer Induction: Nitrates as Independent Risk Factors or Risk Modulators after Radiation Exposure, with a Focus on the Chernobyl Accident

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Abstract
In recent decades, differentiated thyroid cancer (DTC) incidence has been increasing worldwide. The important contributions to this phenomenon of "overdiagnosis" driven by wider use of improved ultrasound systems are amply documented, notwithstanding the "real" carcinogenic effects of ionizing radiation, e.g., from the Chernobyl accident or health care interventions. Less well understood is the role of nitrates – as environmental pollutants, in diet, and in medication – in thyroid carcinogenesis. Increasing exposure to nitrates is associated with rising incidence of esophageal, stomach, bladder, and colon cancers. Recent data suggest that in agricultural areas with higher mean nitrate levels in groundwater, DTC risk is also elevated. Our work in Belarus after Chernobyl has shown that children in districts with high nitrate concentrations in drinking water had significantly higher thyroid cancer incidence after irradiation than did their counterparts in areas with lower nitrate concentrations. Notwithstanding thyroid shielding, increasing use of computed tomography and dental X-rays heightens radiation exposure of the salivary glands in the general population, especially in children and adolescents. When nitrate intake is increased, salivary gland irradiation may potentially result in carcinogenic elevations in plasma nitric oxide concentrations. In conclusion, excess nitrate intake seems to be an independent risk factor for DTC. Additionally, we hypothesize from our data that high nitrate levels modulate the carcinogenic effect of radiation on the thyroid. Cohort studies, case-control studies, or both, are needed to quantify the effects of nitrates on DTC risk in the presence or absence of radiation exposure, e.g., that associated with diagnostic or therapeutic health care interventions.

Introduction

During the last 30 years, the incidence of differentiated thyroid cancer (DTC) has steadily increased worldwide, most markedly in France, Italy, the Republic of Korea, Australia, and the USA [1–8]. In the USA, DTC incidence

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is rising more rapidly than that of any other malignancy except liver cancer [1], with the annual percent change (both genders) increasing from 2.4% in 1980–1997 to 6.6% in 1997–2009 [2, 8]. In Europe, the increase in the last 2–3 decades has ranged from 5.3% (Switzerland) to 155.6% (France).

In Belarus and Ukraine, DTC incidence has also substantially increased in the past 25 years; there is strong evidence that this increase was mainly due to radiation exposure of children and adolescents after the Chernobyl accident [9–11]. Nonetheless, an appreciable proportion of thyroid cancers diagnosed in young people in these countries may be related to screening or other confounders [10, 12].

The main factors contributing to the worldwide increase in the incidence of DTC continue to be debated. Today, it is generally accepted that the widespread use of ultrasound, introduced in the 1980s to diagnose structural thyroid diseases, has led to earlier, more frequent detection of this neoplasm. Better diagnostics were estimated to account for 60% or more of DTC diagnoses in 2003–2007 in women under the age of 80 years in France, Italy, the USA, Australia, and the Republic of Korea, and 30% or more in other very high-income countries [13]. Consistent with these estimates, small thyroid cancers that are best discovered using new technologies (ultrasound and fine-needle aspiration biopsy) have shown a sharply increased incidence [14]. However, improved medical surveillance and "overdiagnosis" do not completely explain the rise in rates of papillary thyroid carcinoma (PTC), since a significant increase also has been observed for larger tumors (>10 mm) [15–18].

DTC and Radiation Exposure

Also well accepted as an explanation for greater frequency of DTC diagnoses is radiation exposure. External radiotherapy in childhood for cancer, tinea capitis, or an enlarged thymus or tonsils has been long known to be associated with an elevated risk of DTC [19–21]. Additionally, DTC was the first solid tumor to be found in excess among atomic bomb survivors in Japan [22]. An updated pooled analysis of 12 studies [23] identified a consistent risk model across the full range of external radiation doses to the thyroid, with relative risk (RR) increasing approximately supralinearly through 2–4 Gy, and then leveling and declining above approximately 30 Gy, although RRs remained elevated. Radiogenic effects occurred for both PTC and nonpapillary thyroid tumors. For doses >0.10 Gy, RRs increased significantly with dose ($p < 0.01$), with no significant departure from linearity. The excess relative risk (ERR) estimate per Gy was significant within 10 years of radiation exposure at 2.76 (95% CI: 0.94–4.98), and remained elevated 50 years and more after exposure [23].

In several other studies, dental radiography was associated with an increased risk of thyroid cancer [24, 25] and parotid gland tumors [26]. One case-control study [24] found a significant association between self-reported dental X-ray exposure, particularly multiple exposures, and DTC risk (odds ratio [OR]: 2.1, 95% CI: 1.4–3.1, $p < 0.001$) with a dose-response pattern ($p < 0.0001$ for trend). American Dental Association recommendations stress the need to shield the thyroid during dental X-ray examination [27].

Pediatric DTC rates in Belarus began to increase as early as 4 years after the Chernobyl accident [28, 29]. Ecological studies of DTC incidence in Belarus and Ukraine following Chernobyl estimated a linear ERR per Gy of 18.9 and excess absolute risk per Gy of 2.7 [9]. Cohort studies with measurement-based individual thyroid dose estimates reported ERRs per Gy of 5.3 and 2.2 for DTC in Ukraine and Belarus [11, 30–35], respectively.

Nitrates as Pollutants, in Diet, and in Medication

Beyond diagnostic activity and radiation exposure, additional factors may contribute to increased DTC incidence, and require further investigation. In particular, nutritional exposure to chemical pollutants such as nitrates in drinking water, specifically during intrauterine life and early childhood, might affect thyroid cell propensity to mutagenesis. In general, there are five primary sources of exposure to nitrate and its metabolite nitrite: environmental/atmospheric exposure to nitric oxide (NO) and nitrogen, dietary exposure to nitrate and nitrite in food and in drinking water, and endogenous production of NO and swallowing of nitrate-rich saliva [36, 37].

The largest proportion of reactive nitrogen, i.e., NO, nitrogen dioxide, nitric acid, nitrous oxide, nitrite, nitrate, ammonia, nitrogen oxides, and organic compounds such as urea, amines, proteins, and nucleic acids, in the environment comes from agriculture in the form of fertilizers and animal waste [38, 39]. The past 60 years have witnessed an exponential increase in the use of nitrogen-rich manure and reactive nitrogen as fertilizers [40]. Although they boost agricultural productivity, nitrogen-

rich fertilizers let nitrates seep through the soil into both groundwater and surface water. There, these substances can accumulate for years until the concentration is adverse to human health. Because of water pollution, high amounts of nitrate might be present in fruits and vegetables, specifically those grown in greenhouses. Additionally, high nitrate levels may be found in cured and processed meats due to the addition of these chemicals as preservatives or color enhancers. Medications, including antidiarrheals, diuretics, vasodilators, and the cytotoxic chemotherapy agent nitrosourea, also contribute to nitrate exposure in humans [39, 41].

In Belarus, between 1960 and 1990, mean use of nitrogen fertilizers increased more than 20-fold, from 4 to 92 kg/hectare, while the average nitrate concentration in groundwater rose almost 40-fold, from 1.1 to 41.6 mg/L [42]. Groundwater from open wells is the main source of drinking water in rural Belarus. According to the Belarusian Ministry of Health, about 1% of pipeline water samples have nitrate concentration exceeding the World Health Organization (WHO)-recommended maximum contaminant level of 45 mg/L [43]. In contrast, about 40% of water samples from open wells exceed that maximum contaminant level. In Brest and Gomel Oblasts, the proportion of such samples reaches 40–60%, while in Mogilev Oblast, it is about 20% [43].

Physiology and Pathophysiology of Nitrates

In the past 30 years, the roles of NO in physiology and pathophysiology have been extensively studied. Nitrate is metabolized by the nitrate-nitrite-NO pathway. As a gas (in the pure state and under standard temperature and pressure conditions) with an unshared electron, NO participates in various biological processes. In the body, under normal oxygen pressure, NO is produced by NO synthetase from L-arginine. In hypoxia, nitrite is reduced by a variety of reductases, including deoxyhemoglobin, to produce NO. Further reduction/oxidation of NO can lead to metabolite production (nitrogen dioxide, nitrate) [44].

Nitrate and NO are known to affect the iodine metabolism of the thyroid. Nitrate is a competitive inhibitor of the sodium-iodine symporter and prevents iodide uptake by the gland. Thyroid hormone synthesis is thereby compromised, leading to thyrotropin elevation. The resultant chronic thyroid stimulation can lead to proliferative changes, including hypertrophy and hyperplasia as well as neoplasia [45–47].

There are other mechanisms by which ingested nitrate may produce detrimental effects on health. One is through formation of methemoglobin, which inhibits the oxygen-carrying capacity of blood; another is through endogenous formation of N-nitroso compounds that may act as carcinogens [41, 46]. Nitrosamine synthesis depends on temperature and pH, and may be stimulated by low-level gamma radiation [48–50].

The salivary glands play a very important role in the metabolism of nitrate and the nitrate-nitrite-NO pathway [36, 37]. Dietary nitrate is rapidly completely absorbed in the upper gastrointestinal tract. Sixty percent of ingested nitrate is excreted in the urine within 48 h [36, 37]. However, approximately 25% of circulating nitrate is taken up by the salivary glands and secreted into the mouth in saliva. Salivary nitrate concentrations are 10- to 20-fold above blood levels, and may reach several millimolars. Oral facultative anaerobic bacteria, residing mainly in the tongue's crypts, then reduce nitrate to nitrite and NO via nitrate-reducing enzymes. This relatively effective process results in nitrite levels that are 1,000-fold higher in saliva than in plasma.

Nitrates and Radiotherapy

Therapeutic irradiation increases NO levels in salivary gland tissue. NO produced in irradiated tissues mediates cellular regulation through posttranslational modification of a number of proteins [44]. Evidence exists for the role of NO as an intrinsic radiosensitizer [51]. On the other hand, administration of an NO synthesis inhibitor ameliorated the dysfunction of irradiated salivary glands, indicating that NO helps mediate the dry mouth symptoms occurring after irradiation [52].

Radiation-induced bystander effects may be modulated by NO [53–56]. NO synthase activation and NO overproduction after exposure to ionizing radiation not only affect bystander cells with activated NO synthase, but also can stimulate specific cell-signaling mechanisms. These NO-dependent effects include the promotion of genomic instability and the accumulation of DNA reduplication errors in bystander cells, without the direct DNA damage seen in irradiated cells. Hydrophobic properties of NO, permitting the diffusion of the substance through the cytoplasm and plasma membranes, allow this signaling molecule to easily spread from irradiated cells to bystander cells without the involvement of gap-junctional intercellular communication [56].

Nitrate Carcinogenicity: Relation to DTC

The first report of negative health effects of nitrate, namely, methemoglobin formation, was in 1945, after observation of cyanosis in infants in Iowa, USA [57]. Long-term exposure to nitrate and nitrite has been evaluated in relation to multiple tumor types; positive associations were reported for cancers of the esophagus, stomach, bladder, and colon [41, 50].

NO as a carcinogen heavily depends on concentration in a nonlinear manner: the specific activity of this analyte at very low levels blocks tumor growth, while moderate concentrations promote tumor angiogenesis and cell survival via lymphocyte suppression [44]. High NO levels may induce chromosomal breaks directly, or indirectly by inhibiting DNA repair activities [58]. NO can cause irreversible injury to several fundamental cancer control genes. The substance plus superoxide rapidly react to form peroxynitrite, which can cause oxidative damage to DNA. NO can also block DNA synthesis through inhibition of ribonucleotide reductase, the rate-limiting enzyme in DNA production [58–60]. Additionally, NO can directly inhibit enzymes in the mitochondrial electron transport chain or act indirectly by interfering with DNA repair mechanisms, leaving the cell susceptible to other DNA-damaging agents [59]. NO has been shown to have a role in stimulating vascular endothelial growth factor-D (VEGF-D) expression in vitro [61]. The formation of the NO biomarker, nitrotyrosine, was also correlated with VEGF-D expression in human PTC. In that setting, NO may induce lymph node metastasis via VEGF-D stimulation. In vitro, NO has both genotoxic and metastasis-promoting properties. Increased NO generation in cancer cells may contribute to tumor hemangiogenesis or lymphangiogenesis by upregulating VEGF-D [61]. The effects of NO are mediated in part by its metabolites, such as peroxynitrite. Data suggest that NO stimulates CXC chemokine receptor 4 (CXCR4) expression in vitro [62]. Nitrotyrosine formation was also correlated with CXCR4 expression and lymph node metastasis in human PTC [62].

Regarding DTC, Ward et al. [63] found an increased risk of this neoplasm in agricultural areas with higher mean nitrate levels in public water supplies and with longer-term consumption of water with nitrate-N concentrations exceeding 5 mg/L (subjects with ≤5 years' consumption at levels of >5 mg/L, RR: 2.6, 95% CI: 1.1–6.2). Increased dietary nitrate intake was associated with a heightened risk of DTC (RR: 2.9, 95% CI: 1.0–8.1, $p = 0.046$) and with the prevalence of hypothyroidism (OR: 1.2, 95% CI: 1.1–1.4), but not hyperthyroidism [63].

With regard to thyroid radiation dose, de Vathaire et al. [64] investigated potential modifiers of the thyroid dose response to radiation therapy in survivors of pediatric solid tumors other than thyroid cancer. The risk of DTC as a second primary malignancy increased with a thyroid dose of up to 10 Gy, then leveled off for higher doses. The excess RR per Gy of radiation to the thyroid was 4.7 (95% CI: 1.7–22.6). Patients also receiving nitrosourea chemotherapy had a 6.6-fold (95% CI: 2.5–15.7-fold) higher risk than those who did not.

Exposure to Nitrates and Radiation after Chernobyl

Recently published data suggest a synergistic influence of nitrates in drinking water and the thyroid radiation dose on the incidence of childhood DTC in Belarus after the Chernobyl accident [12]. The highest mean thyroid dose (320 mGy) and the highest incidence of pediatric thyroid cancer in 1986–2005 (11 per 100,000 patient-years) was found in the most contaminated area, Gomel Oblast [12]. However, there was a notable exception to the general dose-incidence rate pattern, i.e., substantial difference in rates of pediatric thyroid cancer in Mogilev versus Brest Oblasts (1.50 vs. 5.51 per 100,000 patient-years). Whereas the estimated thyroid doses from iodine-131 were comparable in the two regions (65 vs. 51 mGy), nitrate contamination of drinking water significantly differed (mean levels in open well water, 40 vs. 185 mg/L). Radiation dose was significantly associated with thyroid cancer incidence ($p = 0.029$), but the effect of radiation significantly varied according to the nitrate concentration in drinking water ($p = 0.004$). A plausible interpretation of these observations is that the radiation effect on thyroid cells might be modified by patients' ingestion of nitrate from drinking water [12]. Comparison of maps respectively showing levels of groundwater pollution by nitrates (Fig. 1a) and Chernobyl-related radiation doses (Fig. 1b) also suggests that both factors may influence DTC risk.

Conclusions

Based on our own experience and on published data, we hypothesize that thyroid cancer may be induced by coincidence of several conditions: (1) excessive nitrate uptake via drinking water increases nitrite production,

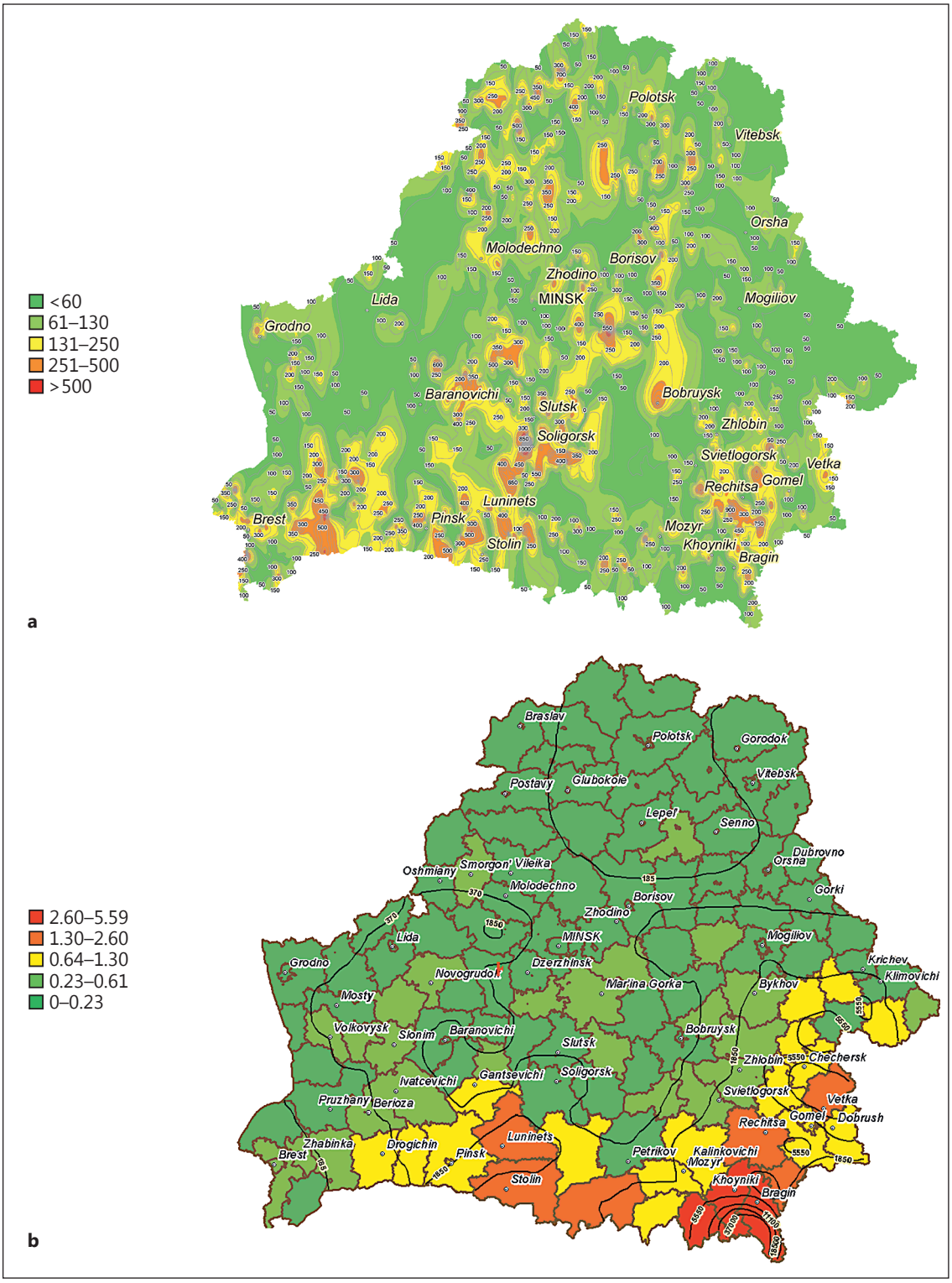

Fig. 1. Maps of Belarus depicting by district (oblast) the level of groundwater pollution with nitrate (mg/L) measured in open wells in 1988–1990 (**a**) and the prevalence (per 1,000) of pediatric thyroid cancer in 1986–2005 in the cohort ages 0–18 years at exposure to radioactive fallout from the Chernobyl accident (**b**). In **b**, areas exposed to such fallout are bounded with black lines, and radioactive contamination due to radioiodine in 1986 (in kBq/m^2) is shown in small numerals. Notably, areas of greatest pediatric thyroid cancer prevalence tend to coincide with areas characterized by both a high radiation exposure and high nitrate pollution of groundwater.

which leads to the development of hypoxia in the blood, especially in children, and to overproduction of NO, which is carcinogenic per se; (2) radiation exposure of the salivary glands, e.g., by dental X-ray examination, may also lead to increased plasma levels of NO; and (3) if one or both of these processes coincide with radiation exposure of the thyroid, the considerably increased NO concentrations in the body presumably enhance the carcinogenic effect of the radiation.

The role of radiation in thyroid carcinogenesis is well documented. The influence of other factors and confounders and their synergistic effects is less well understood. Studies of radiation-induced DTC in Belarus after the Chernobyl accident have shown that children living in areas with high nitrate concentration in drinking water have a significantly elevated thyroid cancer risk. A plausible interpretation is that the radiation effect might be modulated by ingested nitrates. Further cohort studies or case-control studies with individual exposure estimates are required to quantify the effect of nitrate on DTC risk in the context of growing use of medical radiation for diagnostic and therapeutic purposes. Such studies examining the increasing exposure to nitrates alone and in combination with ionizing radiation may provide a better understanding of the considerable increase in thyroid cancer incidence in many countries.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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