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Increasing Incidence of Thyroid Carcinoma: Risk Factors and Seeking Approaches for Primary Prevention

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Based on opinions published by many scientists about the increase in the incidence of thyroid cancer in many countries, this paper intends to identify research to be done on one hand with respect to reasons for this increase, the natural course of thyroid cancer and risk factors and - on the other hand - to support the clinician in primary prevention of thyroid cancer. Along with the traditionally discussed risk factors: ethnicity, heredity, sex effects/hormones, comorbidity, radiation exposure, diet (iodine), life-style (smoking), features of the natural environment, the effect of endocrine disrupters and in particular nitrates are also discussed. For the clinician, a simple approach for primary prevention of thyroid cancer is to refer the patient for a radiological examination applying ionizing radiation with exposure of the head and neck region only if the indication is justified according to the International Committee for Radiological Protection. In clinical practice, it is also important to take into account and minimize other risk factors: prevention of obesity and weight reduction, adequate treatment of various thyroid diseases, avoidance of excessive consumption of nitrates and other endocrine disruptors/ environmental pollutants. In case of a nuclear emergency, attention has to be paid for immediate withdrawal of contaminated food and drink as well as iodine thyroid blocking especially in vulnerable members of the population as children, pregnant or breastfeeding women. More research is also required to identify other reasons of the increasing incidence and predictors of aggressive vs indolent behavior of thyroid cancer to avoid unnecessary screening activity, overdiagnosis, and overtreatment.

Key Words: Thyroid carcinoma, Risk factors, Screening, Radiation, Nitrate, Prevention

Introduction

An increase in thyroid cancer incidence since the late 80's is higher than in any other cancer. Many studies have demonstrated that screening with ultrasonography is an important occasion contributing to this rise.[1-3] The increase of thyroid cancer incidence however may not be completely dependent on screening only. It has to be reviewed that the exposure to known and unknown risk factors like radiation, lifestyle changes, and environmental pollutants contribute to the increase of thyroid cancer incidence. It is also believed that overdiagnosis may be a result of thyroid screening activity. Even with generally favorable prognosis, early diagnosis of thyroid cancer and its benefits have been discussed and new clinical approaches for active surveillance of thyroid microcarcinoma are suggested. This paper intends to contribute to this discussion addressing research to be

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done with respect to risk factors for thyroid cancer other than exposure to radiation, the natural course of disease on one hand and to support the clinician in primary prevention of thyroid cancer on the other.

Epidemiology of Differentiated Thyroid Cancer

Over the last three decades, the incidence rate of thyroid cancer has steadily increased in different regions,[4-7] most significantly in South Korea, Italy, France, the United States, and Australia.[8-11] The growth rate of thyroid cancer incidence is higher than any other malignant tumor in the United States along with liver cancer.[4] According to the study by Lim et al.[11] from the Surveillance, Epidemiology and End Results (SEER) program, an average increase in thyroid cancer incidence during 1974-1977 was 4.56 per 100,000 person-years, and significantly higher - 14.42 per 100,000 person-years during 2010-2013. Interestingly, the sharpest increase of annual percent change (APC) with 12.2% (10.6-13.8%) was found for papillary thyroid cancer (PTC) with a diameter of less than 1 cm between 1998 and 2003. However, the incidence of tumors larger than 4 cm of diameter increased as well (e.g. with an APC increase of 6.9% (6.2-7.6%).[11] According to incidence data for five continents made available by the WHO International Agency for Research on Cancer in Lyon,[12] there are other countries with even steeper increases of thyroid cancer incidence during the last 30 years; among them are Italy and Korea. For Italy, the data originates from smaller local registries in the country and is not comparable to high coverage data as in the US registry. The figures for Korea result from mass screening and will be discussed below in section 3. The incidence of thyroid cancer after the Chernobyl accident in the past 25 years is increased markedly in Belarus and Ukraine, see section 4.2.

The increase of thyroid cancer incidence among children has been announced in some countries. In the US, the study by Qian et al.[13] using the SEER database from 1973 to 2013 among 1806 individuals younger than 20 years reported that the incidence rates of thyroid cancer in this period of time increased from 0.48 to 1.14 per 100,000 person-years. APC was 1.11%; (95% confidence interval [CI], 0.56-1.67%) from 1973 to 2006 and then substantially enlarged to 9.56%; (95% CI, 5.09-14.22%) from 2006 to 2013. McNally et al.[14] found that in northern England the standardized incidence rates of thyroid cancer rose from 0.2 to 0.6 per million in male aged 0-14 years from 1976-1986 to 1997-2005, and from 0.3 to 0.5 per million in female children. According to Korea Central Cancer Registry, the crude incidence of pediatric thyroid cancer between 1999-2012 grew from 0.5 to 1.7 per 100,000 and the proportion among different type of cancers increased from 4.4% to 10.6%.[15]

Of note, the difference in autopsy prevalence of thyroid carcinoma (or microcarcinoma) from 0.01% in USA to 35.6% in Finland is very high and might be primarily related to methods used for slicing of the thyroid and histological examination.[16,17] In a meta-analysis of the prevalence of differentiated thyroid cancer (DTC) with dissection of the whole gland in autopsy studies, the mean prevalence of DTC with 11% was stable from 1975-2001, however with large fluctuations hampering the interpretation of results.[18]

Screening and Overdiagnosis

Many publications have demonstrated that reasons for thyroid cancer incidence rise worldwide are mainly due to expansion in screening and enhancements in diagnostic process for detecting small nodes resulting in "overdiagnosis", meaning that otherwise indolent cancers are identified which would not have caused clinical symptoms or death due to this disease.[3,9,10] The American Thyroid Association (ATA) released an updated Guideline in 2015, suggesting screening people with familial follicular cell-derived DTC may contribute to a diagnosis of thyroid cancer at an early stage. However the panel did not recommend "for or against ultrasound screening because there are no proofs of reducing morbidity or mortality".[1] The US Preventive Services Task Force (USPSTF) in 2017 stands "against screening for thyroid cancer in asymptomatic adults".[2] Clinicians were advised neither to

use neck palpation nor ultrasonography or other techniques and that the "harm from such screening in asymptomatic persons can outweigh any benefits". In the same time, the USPSTF acknowledges that reasons of increase in the risk for thyroid cancer could be related to preventive medical examinations, a history of radiation exposure, family history of thyroid cancer (familial medullary thyroid cancer or multiple endocrine neoplastic syndrome).[2)]

However, real reasons promoting to the thyroid cancer "epidemic" are more complex, seeming to be multifactorial and the main explications for this increase are still under discussion. Some of them are associated with widespread practice of ultrasound and fine-needle aspiration (FNA) for assessment of small thyroid nodules. The first experience of implementing ultrasound mass screening programs for detection of thyroid cancer was acquired after Chernobyl. The results of this screening will be discussed in sections 4.2 and 5.5.

The thyroid cancer incidence rose in Korea from 10.6 in 1996 to 111.3 per 100,000 in women in 2010, and it rose from 1.9 to 27.0 per 100,000 in men in the same period of time. The numbers indicate a 25% annual increase over the past decade after mass screening was introduced in Korea.[19)] Between 2007 and 2010 the mortality of thyroid cancer was 0.7 per 100,000 people. Screening has been associated with increased diagnosis of thyroid cancer (r=0.74 [95% CI, 0.59–0.88]); but was not linked to mortality (r=−0.08 [95% CI, 0.59–0.63]) due to this disease.[20)] According to study based on Statistics Korea by Choi et al.[21)] the age-standardized mortality rates (ASMRs) of thyroid cancer elevated from 0.17 (95% CI, 0.17–0.18) to 0.85 (95% CI, 0.83–0.86) per 100,000 in period of time between 1985–2004. It was the highest rate among all countries. Between 2004 and 2015 the ASMRs declined to 0.42 (95% CI, 0.41–0.43) per 100,000. The authors gave estimates of the APC 7.94 (95% CI, 6.43–9.46) from 1985 to 2004, and −4.10 (95% CI, −5.76 to −2.40) between 2004 and 2015. Also the authors believe that some factors like changes in lifestyle, standardization of diagnosis and treatment of thyroid cancer could be related to the decline in thyroid cancer mortality in Korea.[21)] Korean multicenter cohort study by Jeon et al.[22)] demonstrated decreasing disease-specific mortality of DTC in period 2 (2001–2003) and 3 (2004–2005) compared to that of period 1 (1996–2000). The authors found that the size of the tumors and the portion of high-volume lymph node metastases have become smaller with period of follow-up.[22)] These findings suggest a possible benefit of early diagnosis of small thyroid cancer.

According to Korea Central Cancer Registry, the crude thyroid cancer incidence among children (0–19 years) from 1999 to 2012 increased 3 times.[15)] According to Cho et al.[15)] at Samsung Medical Center between 1995 and 2013, among operated 126 children with thyroid cancer, 91 cases (72%) were diagnosed by palpation and the only 28% was identified by imaging studies. Thus, in children, most tumors are detected by palpation, but not by ultrasound.

According to estimates by Vaccarella et al.[10)] thyroid screening could be related to 60% or more of all thyroid cancer cases in women diagnosed between 2003–2007 in Italy, France, the United States, the Republic of Korea, and Australia and about 30% in other high-income countries. Some studies emphasized that thyroid cancer incidence correlated with employment, white-collar jobs, higher household income, education, and health insurance coverage, and other socio-demographic markers such as number of doctors in the area (endocrinologists, surgeons, radiologists).[23–25)]

It should be noted, that application of thyroid ultrasonography and FNA, increased medical surveillance, could not completely elucidate the increase in incidence of PTC because a significant rise was discovered for larger tumors.[8,11,26,27)] The authors conclude that these findings indicate a real increase in thyroid cancer incidence in the United States, because such large tumors are not "silent" and are not only detectable by ultrasound but will be diagnosed by inspection and palpation of the neck or cause complaints for the patient. In addition, the clinical relevance of such large tumors can be derived from the circumstance, that for this subgroup thyroid cancer related mortality is increasing over time.[8,11)]

In regards to the screening effect, Lin et al.[28)] con-

cluded that there are still "no data related to clinical trials that examined the results of screening for morbidity or mortality of thyroid cancer, compared to the absence of screening". Also, there aren't any "data related to the harms of thyroid cancer screening, as well no studies examined the effect of overdiagnosis in a screened versus unscreened populations". According to Jung et al.[29] in representative study for thyroid cancer screening in Korea (NEST), 1.1% of patients died in the screening group compared to 4.1% in the clinical detection group during follow-up 9.4 years ($p<0.001$). The authors believe that screening was related to a decrease in mortality in the advanced stage of thyroid cancers, however not in the early stage of the disease.

Radiation as a Well-Known Risk Factor

Medical Radiation Exposure

Many studies have demonstrated that different kinds of cancers in children are more likely than in adults to be caused by radiation. Even small doses, less than 50-100 mGy may increase the risk of childhood thyroid cancer, with a linear dose-response up to 10-20 Gy. The excess risk remains after exposure for more than four decades.[30-34]

External radiotherapy in children for different type of cancer, enlarged thymus and tonsils, tinea capitis might raise the risk of thyroid cancer.[30,31,35-37] An updated pooled analysis of 12 studies by Veiga et al.[38] demonstrated a risk model of external radiation doses to the thyroid in children, with relative risks (RR) rising supralinearly through 2-4 Gy, then leveling and decreasing above 30 Gy.

In the United States exposure to medical diagnostic X-rays has increased considerably until 2006, from an estimated mean per capita effective dose of 0.54 mSv (1980) to 3.0 mSv (2006) and then decreased slightly to 2.3 mSv (2016). The frequency of computerized tomography (CT) scans, nuclear medicine examinations and other radiologic procedures grew about 10-fold between 1950-2006, accounting to about 50% of increased exposure.[39-41] In Germany the estimated mean per capita of "medical" effective dose is increasing as well and in 2014 reached 1.6 mSv. The application frequency of CT scans was 9%, however CT contributed 1 mSv (=62%) to the increasing per capita dose from all sources.[42]

To give an estimate of the radiation risk for the thyroid involved with CT, it is more appropriate to focus on organ doses instead on effective doses. The dose to the thyroid involved with neck CT may reach up to 80 mGy.[43-55] Modern CT techniques with e.g. automatic tube current modulation and the thyroid bismuth shielding may mitigate thyroid doses by 40-80%.[43-45] For cerebral angiography, thyroid doses as high as 250 mGy are reported.[46] The use of CT with iodinated contrast enlarges the radiation-absorbed dose by the thyroid gland by up to 35%.[47] A population based case-control study by Zhang et al.[48] provides first accurate evidence that nuclear medicine procedures and CT scans may be responsible for an increased risk of thyroid cancer in adults. According to Zhang et al.[48] any type of diagnostic radiography was associated with an increased risk of tumor size ≤10 mm, (odds ratio [OR]=2.76, 95% CI, 1.31-5.81). The authors concluded that in the US population 37-85% of well-differentiated thyroid microcarcinomas could be linked to medical radiation exposure.[48] The weakness of Zhang's study is that the information on diagnostic X-ray exposures was collected on self-reporting. A recent massive study of 12 million youths in Korea also raises troubling questions about the increased thyroid cancer risk (IRR, 2.19 [95% CI, 1.97-2.20]) at very low doses of radioactivity during diagnostic procedures.[49]

In several publications, dental X-ray examinations have been linked to an increased thyroid cancer risk[50,51] and tumors of the parotid gland as well.[52,53] An increased risk of thyroid cancer has been described in diagnostic X-ray workers, dentist's assistants, and radiology technicians.[54,55] The case-control study by Memon et al.[50] found that self-reported dental X-ray examinations (particularly multiple) were significantly associated with the risk of thyroid cancer (OR=2.1, 95% CI, 1.4-3.1, $p<0.001$). In this regard, recommendations by the American Dental Association stress the requirement "for shielding of the thyroid during

dental X-ray" examination.[56] The results of recent meta-analysis by Han and Kim[57] indicate that diagnostic radiation exposure is associated with an increased thyroid cancer risk: for overall exposure to diagnostic radiation exposure (OR=1.52 [CI 1.13-2.04]); by type of exposure, exposure to computed tomography scans (OR=1.46 [CI 1.27-1.68]), dental X-rays (OR=1.69 [CI 1.17-2.44]), head and neck (OR=1.31 [CI 1.02-1.69]) and chest (OR=1.71 [CI 1.09-2.69]).

Radiation Exposure from Atomic Bombing, Nuclear Accidents and from Nuclear Facilities in the Past

Numerous studies indicated the serious health consequences of the atomic bombing in Hiroshima, Nagasaki, Nevada, Marshall Islands, Semipalatinsk, Nowaja Semlja.[58-61] Thyroid cancer was among the first solid cancers that arose after the atomic bombing in Japan.[59,60] The highest risk of thyroid cancer was among of atomic bombs survivors in Hiroshima and Nagasaki younger than 10 years old, in the older subjects the risk was considerably smaller.[61]

The consequences of exposure from fallout after the Russian nuclear tests in Nowaja Semlja and the incidence of thyroid cancer were studied in Norway and Sweden by Lund and Galanti.[62] The authors found that the RR of developing thyroid cancer was higher for exposed cohorts (born 1951-1962), compared to ones not exposed (born 1963-1970).

According to WHO experts, the most serious long-term consequences of the Chernobyl in Belarus, Ukraine and Russia were about 11,000 thyroid cancers cases among those who were exposed to radiation in childhood at the time of the accident.[63,64] The number of pediatric thyroid cancer in Belarus began to increase dramatically around four years after the Chernobyl accident.[65,66] Ecological studies in Ukraine and Belarus found that thyroid cancer risk after the Chernobyl estimated a linear excess relative risk (ERR)/Gy of 18.9 and excess absolute risk (EAR) per Gy per person year of 2.66.[67-69] Case-control studies in Belarus and Russia among exposed children with individual thyroid dose estimates of 131I reported ERR per Gy between 4.2 and 7.2.[70,71] Cohort studies based on individual thyroid dose estimates published ERR/Gy of 5.25 for thyroid cancer in Ukraine[72,73] and 2.15 for Belarus.[74,75] Many post-Chernobyl studies detected the rising thyroid cancer risk with declining age at ^{131}I exposure.[69,76] An international consensus found, the risk of radiation induced thyroid cancer substantially increases at doses more than 100 mSv.[7,77,78]

Some studies support an association between residence in the proximity to nuclear power plant (NPP) or an exposure event from one of the nuclear reactors in the United States and the incidence of thyroid cancer.[79,80] According to a study of individuals residing near NPP in France, the thyroid cancer incidence was comparable to control groups.[81] The study of Davis et al.[82] gave no arguments, that the release of 131-iodine from the Hanford site (USA) increased the incidence of thyroid cancer. A meta-analysis of epidemiologic studies was conducted by Kim et al.[83] to examine the risk of thyroid cancer with respect to residing near NPP. The authors found no significant association: standardized incidence rate (SIR)=0.98 (95% CI, 0.87-1.11), standardized mortality rate (SMR)=0.80 (95% CI, 0.62-1.04). But sensitivity analysis by exposure definition demonstrated that residing less than 20 km from NPP was connected to significant increase in the risk of thyroid cancer, OR=1.75 (95% CI, 1.17-2.2).[83] A thyroid cancer mortality increase has been described for British Workers at Sellafield multi-function nuclear site.[84]

New Observations from the Fukushima Nuclear Accident

A new challenge to explore the carcinogenic effect of ionizing radiation on thyroid cancer is the Fukushima Daiichi NPP accident.[85] A large-scale thyroid ultrasound examination (TUE) survey started in 2011 for children and adolescents aged 18 years or younger at the time of the accident. Large-scale ultrasound mass screening in Fukushima Prefecture detected unexpected high thyroid cancer prevalence in young subjects. For comparison, some researchers in post-Chernobyl studies found that thyroid cancer incidence may rise by a factor of 3-7, which may be at least partially interpreted by screening or increased

surveillance.[69,78,86,87]

According to Suzuki et al. in the TUE survey,[88,89] 300,476 subjects were included. In three rounds of screening survey 152 thyroid cancer cases were operated with average age of patients being 17.8 years. The average tumor size was 14.9 mm (among them 16.5% with tumor diameters >2 cm). Postoperative lymph node metastases, extra-thyroidal invasion, and pulmonary metastases were detected in 80.0%, 42.1%, and 2.6% of patients, respectively. Hemi-thyroidectomy was performed in 91.7%, total thyroidectomy in 8.3%, lymph node dissection of the central compartment in 84.8% and of the lateral compartment in 15.2% of all cases. It should be noted that lymph node metastases were visualized by ultrasound only in 19.3% cases.[88,89] For comparison, the clinical data of 1078 post-Chernobyl pediatric patients 4-18 years of age at diagnosis with all types of PTC born before April 1, 1987 in Belarus operated in 68.6% with total thyroidectomy, revealed mean tumor size of 14.4±10.6 mm, N1 stages with lymph node metastases in 73.7% and M1 stages with pulmonary metastases in 11.1%.[90] So interestingly, the percentage of patients needing thyroid surgery with lymph node metastases after Fukushima and Chernobyl was very similar (80% vs. 74%).

The findings from the TUE elevated concerns among the medical community and residents of Fukushima that it could be related to the radiation accident at Daiichi NPP.[91] According to the studies reported, thyroid cancer cases in Fukushima survey cannot be directly associate with the effects of radiation, because 1) The thyroid doses in Fukushima with <1 mSv and maximum 50 mSv were much lower than those in Chernobyl (median 300 mSv, 95% of doses higher than 50 mSv;[92] 2) The period between exposure and detection of thyroid cancer in Fukushima was shorter as in Chernobyl with 4 years; 3) Thyroid cancer patients in Fukushima were much older than the Chernobyl children with mean age of 16 years and 8 years respectively.[91,92]

On the other hand, it is understandable that concerns in the population and open questions of scientists about the "thyroid cancer epidemy" after the Fukushima disaster continue to exist because it is unclear why such a high number of clinically relevant thyroid cancer cases with lymph node metastases is observed. According to Yamashita et al.[91] "further follow-up of the Fukushima cohort may provide unique insights into the incidence and natural history of PTC in young individuals including potential risk factors other than radiation".

Other Endogenous and Exogenous Risk Factors or Confounders

Ethnicity, Heredity, Sex Effects/Hormones, Comorbidity

The comprehensive interactive data set of Cancer in Five Continents[93] allows us to check for differences in the incidence and mortality of cancer related to regions and countries worldwide. The search for incidences in 2018 shows the well-known mass screening effect with incidences higher than 2-fold for Korea as compared to the rest of the world. The USA and Italy follow the incidence statistics as generally high-income countries. Within the USA, thyroid cancer incidence seems to lower in citizens of African or Hispanic origin. For Israel, thyroid cancer incidence seems to be higher in the Jewish population as compared to the non-Jewish population. These observations from the USA and Israel again are explainable by better access to medical care. Keane et al.[94] in a systematic review stated: "The variations amongst incidence and outcomes of thyroid cancer in racial groups are most likely a result of a number of interrelating factors, including genetic, environmental and modifiable lifestyle factors".

Individual susceptibility and heredity could increase the thyroid cancer risk. They include familial adenomatous polyposis (Gardner Syndrome), Carney complex type 1, Cowden syndrome and Werner syndrome.[95] Familial adenomatous polyposis could associate with 1-12% of the lifetime thyroid cancer risk,[96] in PTEN hamartoma tumor syndrome – with 35%.[97] In patients with DICER1 syndrome, the risk of

developing thyroid cancer may be 16 times higher than in the population.[98]

A strong association for susceptibility to thyroid cancer was disclosed for rs965513 (PTCSC2/FOXE1) in chromosome 9q22.33.[99] A genome-wide association study by Takahashi et al.[100] has shown a strong association of SNPs also in the FOXE1 region in Chernobyl cases of thyroid cancer, however no specific markers for radiation-induced thyroid cancer have been detected.

Many studies have proven, that thyroid cancer in women is more frequent than in men, with a ratio of around 1:1 before and 3:1 after puberty. This difference can be explained by hormone metabolism in the thyroid cancer etiology and possibly increased health awareness in women.[101-103] A recent comprehensive review addressed the issue of estrogen activity in the thyroid was shown the strong proof for its capability to manage reactive-oxygen species (ROS) generation. The authors hypothesize that in women the higher thyroid cancer susceptibility could be due to higher ROS levels resulting in oxidative DNA damage accumulation.[104]

Comorbidity and individual susceptibility may also be considered as etiologic factors of thyroid cancer. Recently a meta-analysis of twelve prospective observational studies by Liang et al.[105] showed association of benign thyroid diseases with thyroid cancer risk. The authors found that the pooled SIR of thyroid carcinoma was for goiter 7.65 (95% CI, 6.94-8.37), for hyperthyroidism 5.96 (95% CI, 1.88-10.03), for thyroiditis 3.25 (95% CI, 1.62-4.89), and for all benign thyroid diseases 5.98 (95% CI, 4.09-7.86).[105] The results of a Denmark Nationwide population-based registry study demonstrated an increased risk of thyroid cancer in patients with diagnosis of thyroiditis and hyperthyroidism that cannot be completely associated with greater medical surveillance.[106]

Obesity is a well-described risk factor for thyroid cancer.[107] Obesity incidence has increased among US population 3-fold between 1960 and 2012, paralleling trends in thyroid cancer incidence.[108] The relation of obesity to thyroid cancer remains under discussion. Schmid et al.[109] conducted a meta-analysis of thyroid cancer risk and adiposity measures. The authors analyzed data on 12,199 thyroid cancer patients and found that the thyroid cancer risk in overweight persons is 25% greater and in individuals with obesity - 55% greater than their normal weight peers.[109]

Diet (iodine), Life-style (smoking)

Nutritional iodine deficiency could be one of the factors that might elucidate significant differences in thyroid cancer incidence in different areas and countries.[58,110] However, change of iodine intake in population does not effect the overall risk for thyroid cancer directly, but modification of iodine deficiency might shift the subtypes of thyroid cancer from follicular and anaplastic toward less malignant papillary forms.[110] Some studies demonstrated an interconnection between increasing thyroid cancer prevalence and increasing iodine intake levels in the population over the years since iodine supplementation began.[111,112] However no differences in two Hungarian regions with different iodine intake were shown in the autopsy study of Kovacs et al.[113]

Recently Cao et al.[114] carried out a meta-analysis of 8 case-control studies (2213 cases; 2761 controls) to estimate the association between the thyroid cancer risk and iodine intake. The authors found that excess iodine intake (>300 mg/d) related to the reduced risk of thyroid cancer (OR=0.74, 95% CI, 0.60-0.92) and was as a protective factor.[114] Another meta-analysis by Lee et al.[115] of association between iodine intake and prevalence of PTC has demonstrated a higher iodine exposure in thyroid cancer patients compared with controls, especially in regions with high iodine supply. The authors found a positive association between the thyroid cancer risk and iodine exposure. The OR for high iodine exposure and the thyroid cancer risk was 1.41 (95% CI, 1.05-1.90) and even higher in high iodinated regions - (OR=2.20, 95% CI, 1.38-3.48).[115] These studies demonstrate considerable controversy between iodine intake and PTC risk.

Several studies have report a protective effect of smoking. According to Kitahara et al.[116] "current smoking consistently has been associated with a 30% to 40% reduction in thyroid cancer risk in USA, in-

dependent of obesity and other risk factors". The "protective" effect of smoking is stronger and dose related in current smokers, may be associated with estrogen metabolism.[117-119] Smoking is significantly associated with lower exhaled nitric oxide level possibly reducing the risk for thyroid related to nitrate/nitrite, see section 5.5.[120,121] To summarize, obesity has to be considered as a proven thyroid cancer risk factor whereas the role of smoking as protective factor remains to be corroborated.

Risk Factors of the Natural Environment

It has been described that some environment factors, like volcanic activity, could be associated with increased thyroid cancer risk. Also exposure to heavy metals and/or natural radioactivity may play a role. For instance, in volcanic area of the Mount Etna the thyroid cancer incidence is two times higher than the rest of Sicily, and mainly the papillary type of thyroid cancer is elevated.[5,122-124] High figures of thyroid cancer are registered in Iceland and Hawaii and a possible association with volcanic activity has been suggested.[123-125] In volcanic areas of the Pacific Islands, the age-standardized rate of the thyroid cancer incidence is particularly increased, in French Polynesia it was 24.6/100,000 women and in New Caledonia it reached 71.4/100,000 Melanesian women during 1985-1999.[126]

Endocrine Disruptors

In recent decades, the population is increasingly exposed to endocrine disruptors, environmental pollutants like pesticides, asbestos, benzene, polychlorinated biphenyls (PCB), formaldehyde, polyhalogenated aromatic hydrocarbons (PHAHs), bisphenol A (BPA), and nitrates. Many of these chemicals could be carcinogens. For example, flame retardants consisting of polybrominated diphenyl ethers (PBDEs) may stimulate precancerous proliferation of thyroid cell. Endocrine disruptors can mimic, block or overstimulate naturally occurring hormones (thyroid hormones, estrogens, and androgens) or their receptors. Exposure to endocrine disruptors during intrauterine life and early childhood could promote thyroid cell mutagenesis.[6,127] New data from the US Agricultural Health Study reveal that thyroid cancer risk is elevated in agricultural workers using pesticides.[128]

Nitrate and Radiation as Possible Interacting Carcinogens

Besides the radiation exposure, nitrates are discussed as a risk factor for developing thyroid cancer.[129-131] Environmental endocrine effects caused by nitrates have received increasing attention over the last 15 years. Nitrate can interfere with steroid and thyroid hormone homeostasis, reproductive and developmental endpoints as environmental endocrine disruptor.[132] Over the past hundred years, human activity through the use of nitrate fertilizers and the combustion of fossil fuels have doubled the natural nitrogen level onto land.[129,133-135] In the United States the maximum contaminant level (MCL) of public drinking water for nitrate is 10 mg/L as nitrate-nitrogen (NO3-N). In accordance with the World Health Organization (WHO) guideline, nitrate standards for drinking water are 50 mg/L as NO3 or 11.3 mg/L NO3-N. These nitrate regulations have been developed for the prevention of infant methemoglobinemia; however cancer and other adverse health consequences were not considered.[129]

Also Ward et al.[136] studied the risk of thyroid cancer in Iowa's agricultural areas with higher average nitrate levels (>5 mg/l nitrate-N) in public water supplies. The authors found that RR for thyroid cancer of 2.6 (95% CI, 1.1-6.2) was increased with consumption of water above 5 mg/L nitrate-N for time longer than 5 years.[136] It should be stressed that the carcinogenic effect of nitrate in drinking water is higher than that of nitrate in food because of faster resorption of water and lack of protective antioxidants as e.g. vitamin C, which are available in vegetables and fruit.[129] A meta-analysis of Xie et al.[137] included these studies and stressed the observation that dietary nitrate is a significant risk factor for developing thyroid cancer. Exposure-based assessment of cancer risk due to nitrate in United States drinking water showed that it could be from 0.8 to 2 percent of the annual US thyroid cancer cases, leading to an additional 369-1047 thyroid cancers.[138]

Orita et al.[139] performed in Kawauchi village (Fukushima prefecture, Japan) an examination of nitrate concentrations in drinking water. The average nitrate-N level was 0.62 mg/L (0.20-2.51 mg/L), which was in the normal range.[139] The authors concluded that the examinations of dietary nitrate intake also are required for better understanding of the situation with the increased incidence of thyroid cancer in Fukushima.[139]

Data published from our group demonstrated a synergetic effect of nitrate in drinking water and exposure to radioiodine after the Chernobyl accident on the prevalence of childhood thyroid cancer in Belarus. In Belarus, from 1960 to 1990, the average nitrate level in drinking water multiplied about 40-fold, from 1.1 to 41.6 mg/L. It is related to the increase in usage of nitrogen fertilizers from 4 to 92 kg/hectare.[130,131] Our study[130] demonstrated that in Belarus children from Gomel region received the highest thyroid doses after Chernobyl (320 mGy). The incidence of childhood radio induced thyroid cancer (11 per 100,000 PY) was the highest exactly in Gomel region. However, the incidence also increased in the Brest region (5.51 per 100,000 PY), where the thyroid doses were lower (51 mGy), than in Mogilev region (65 mGy, with incidence 1.50 per 100,000 PY). A reasonable explanation could be addressed to the level of nitrates in drinking water. The highest in Belarus was in Brest region - 185 mg/l, and the lowest, practically within the normal range - in Mogilev region - 40 mg/l. The thyroid cancer incidence was significantly corresponded to the radiation dose (p=0.029). The effect of radiation was altered significantly by a local level of nitrates in drinking water (p=0.004).[130] Moreover the prevalence of radiation induced thyroid cancer among rural children of most contaminated areas (Gomel, Brest, Mogilev) with higher thyroid doses and higher pollution of drinking water with nitrates was significantly elevated in comparison with urban ($p<0.001$).[140]

In addition, we analyzed the data gathered from different screening programs among children after Chernobyl accident in 1990-2005. The prevalence of thyroid cancer in radiation exposed children ranged 0.2-0.6% in Gomel with highest thyroid dose, 0.3% in Brest with lowest thyroid dose and only 0.008% in Mogilev administrative region with a dose similar to, but slightly higher than in Brest. In this way, the analysis of ultrasound screening program results in Belarus showed that the difference in the thyroid cancer prevalence between Brest and Mogilev regions may be related to local environmental condition.[130]

Based on our own experiences and literature data, we hypostasize that the risk for developing thyroid cancer could be addressed to the coexistence of sev-

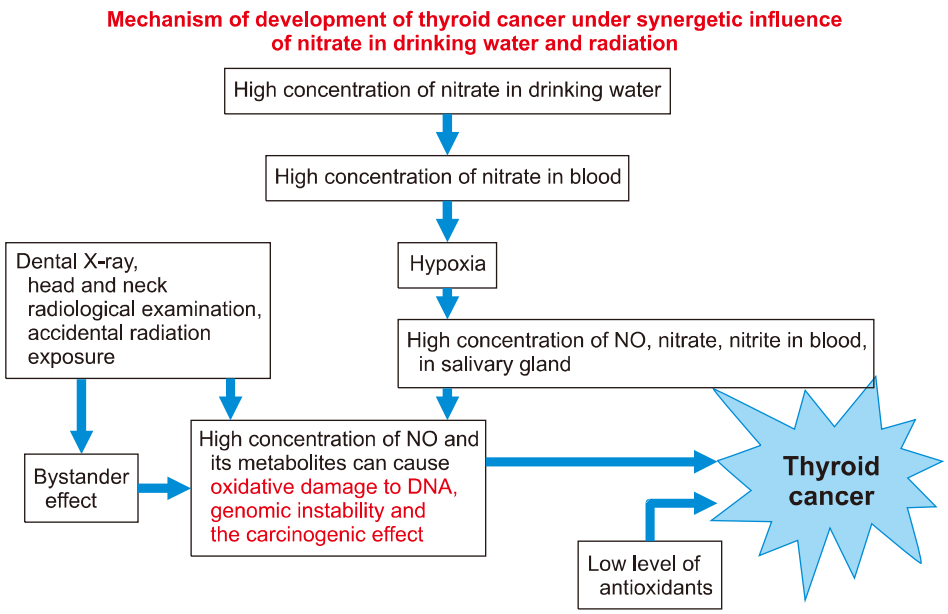

Fig. 1. Scheme of combined effects of nitrate and radiation exposure on development of thyroid cancer. Based on data in Ward et al.[129] and Drozd et al.[130,131]

eral circumstances (Fig. 1): 1) the use of water with an excessive nitrate contamination leads to the development of hypoxia in the blood, especially in children, changes metabolism towards nitrite production and NO, which can cause genomic instability and carcinogenic effect; 2) Dental X-ray, head and neck radiological examination, accidental radiation exposure of thyroid and salivary glands could also lead to increased plasma concentration of NO; and 3) if both of these processes coincide, the substantially increased NO levels presumably enhance the carcinogenic effect of the radiation.[131]

Strategies for Primary Prevention

Without any doubt, thyroid cancer incidence is increasing with approximately 3-5% per year in different countries of the world during the last 3 decades. However, it appears in our opinion, that only 50-60% of this rise can be interpreted by screening only. It is likely that increasing exposure to risk factors like medical radiation, life-style change, and environmental pollutants are considered to play an important role as well.

For the clinician, a simple approach for primary prevention of thyroid cancer is to refer the patient for a radiological examination applying ionizing radiation with exposure of the head and neck region only if the indication is justified according to the International Committee for Radiological Protection[141] following the principle "Choosing Wisely" of the American College of Radiologists[142] or other expert committees. In children and adolescents, this justification that has to be approved by the radiologist is of exceptional importance. Generally, the radiologist should apply low dose CT protocols and image reconstruction procedures up-to-date as well as thyroid shielding for dental radiography and head and neck CT.[34]

In case of a nuclear emergency, attention has to be paid for immediate withdrawal of contaminated food and drink as well as iodine thyroid blocking, especially in vulnerable members of the population such as children, pregnant or breastfeeding women.[143] Mass ultrasound screening for thyroid cancer is not recommended, however programs for individual long-term monitoring should be considered for higher risk individuals (depending on doses, age and other risk factors).[1-3]

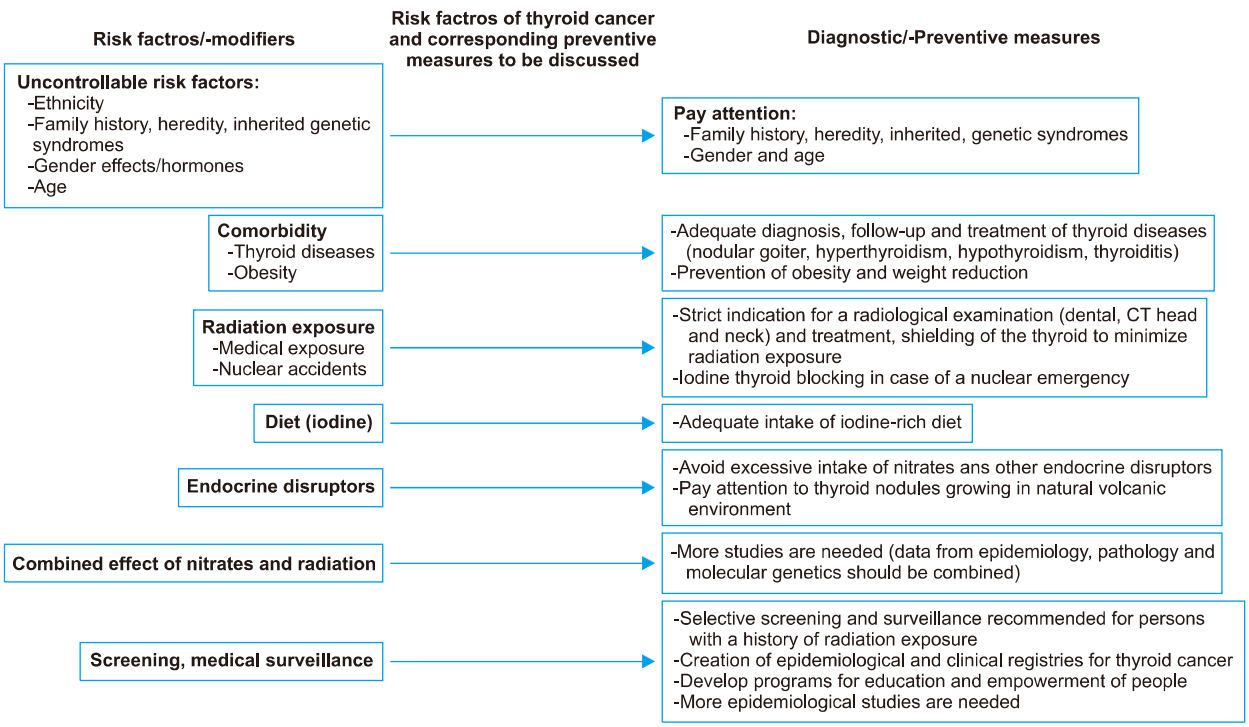

Fig. 2. Risk factors for thyroid cancer and corresponding preventive measures to be discussed. Based on data in Haugen et al.,[1] WHO documents,[3,6,143] Drozd et al.,[130,131] ICRP document[141] and Sinnott et al.[34]

The World Health Organization recommends creating and supporting national cancer registries. Such systems allow keeping records of trends in disease incidence and geographical variation. This is especially important in the case an emergency. WHO also encourages to educate, and engages people to have a more active position in their own health.[3)]

To develop effective preventive measures, more research is needed to better understand the role of endocrine disruptors, specifically on combined effects of nitrates and radiation in thyroid carcinogenesis processes. Based on the known risk factors for thyroid cancer, we tried to present an algorithm that can help clinicians in the early diagnosis and development of preventive measures (Fig. 2).

Generally, the issue of overdiagnosis of thyroid cancer should be discussed more thoroughly. As shown here, a substantial proportion of children operated on for thyroid cancer after the Fukushima disaster – irrespective from radiation as a risk factor – suffers from clinically relevant disease, which cannot be brushed aside with overdiagnosis. Also more research is required to understand which factors predict the behavior of thyroid cancer and classify it as aggressive or indolent. Such research will allow us to avoid overdiagnosis and overtreatment. Better understanding of the influence of various risk factors on the induction of thyroid cancer will help clinicians develop effective strategies for disease prevention.

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Author Contribution

VD, DIB, and CR contributed to the conception, collected the studies, discussed, and wrote the manuscript.

Conflicts of Interest

The authors declare that the study was performed in the absence of any financial or commercial relationship that may be interpreted as a potential conflict of interest.

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