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Papillary Thyroid Cancer in Subjects Who Were Children at the time of the Chernobyl Nuclear Accident: Some Lessons for The Management of Fukushima's Aftermaths

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Abstract

For the past 30 years, we have raised the question of a possible relationship in Belgium between the occurrence of papillary thyroid carcinoma (PTC) and age of children (< 15 y) at the time of the Chernobyl nuclear plant accident in April 1986.

Such a relationship was actually demonstrated from the experience of a surgical team with PTC since the Chernobyl accident.

Radiation exposure affected residents of continental Europe well beyond Ukraine and Belarus. A review of the related scientific literature of the past 30 years demonstrates a persistent higher incidence of PTC among children below 15 at the time of the Chernobyl accident. This relationship with age has been strengthened by the implementation of more sophisticated immunohistochemical technology. Some effective lessons can be drawn for the management of the aftermaths of the 2011 Fukushima nuclear accident, especially for the long term follow-up of populations living in the regions where the radioactive fallouts occurred.

Keywords: Papillary thyroid carcinoma; Surgery; Chernobyl; Fukushima Childhood Cancer; Meteorology

Radiation exposure to the thyroid during childhood is the most clearly defined environmental risk factor associated with malignant thyroid tumours. The risk of thyroid cancer following irradiation is related to radiation dose and age (greater for children exposed early in life), and the risk persists throughout life. Papillary thyroid carcinoma (PTC) is the most common radiation-related histologic type [1-3].

After the Chernobyl accident on April 1986, an increase in the prevalence of childhood papillary thyroid carcinoma was observed in Belarus and Ukraine, only four years after the accident and continuing up to now [4-8]. An increase of childhood thyroid carcinoma was also present, to a lesser extent, in the Russian Federation [9].

The geographical area most contaminated by releases of radioactive iodine from the damaged nuclear reactor of Chernobyl encompassed the site of the Chernobyl plant in Ukraine, and the region around the city of Gomel in Belarus directly to the north of Chernobyl. The increase in thyroid cancer was particularly pronounced among the youngsters at the time of exposure, suggesting that iodine-131 (^{131}I) – the chief component of nuclear accident fallout and an isotope rapidly absorbed by the thyroid gland– was the likely cause of post-Chernobyl PTC in children.

Already in 1997, an extensive clinical and epidemiological study [4] compared the post-Chernobyl thyroid carcinoma in Belarus children and adolescents with naturally occurring thyroid carcinomas of the same age group observed in Italy and

France. The post-Chernobyl Belarus thyroid carcinomas were less influenced by gender, were virtually always papillary, had a greater aggressiveness at presentation, and were more frequently associated with thyroid autoimmunity [4]. The results of this large study support the concept that subjects who were younger at the time of radiation exposure had, and continue to have, a greater risk in developing thyroid carcinoma, and strongly suggest that this age group should be carefully monitored in the future.

The severity of the Chernobyl nuclear accidents had been rated 7 on the International Nuclear Event Scale (INES), the highest severity level, and the same as the March 2011 Fukushima Daiichi nuclear power plant accident. Despite numerous and recurrent official denegation, it is clear, in 2016, that the Chernobyl accident released a massive amount of various radioactive materials, which resulted in radiation exposure of a large number of residents living in former Eastern and Western Europe. Therefore, thirty years after the accident, it remains to ascertain whether the increase in thyroid carcinoma has also extended to adults who were children in April 1986 not only in Belarus and Ukraine but all over Europe.

Previous reports [5-11], on post-Chernobyl thyroid carcinoma focused on patients who were children at the time of diagnosis.

The most striking feature of thyroid cancers observed in Belarus children and adolescents after the Chernobyl accident was the distribution pattern resembling a Gaussian curve [4], with a peak at 10 year, the large majority of the patients (88%) being diagnosed before or at the age of 14 year (mean age at diagnosis was 11.3 ± 3.1). Such an age distribution is in keeping with the concept that the Belarus thyroid carcinoma outbreak was related to a single event, i.e. massive exposure to radiation action within a limited and defined period of time by the short half-life isotope ^{131}I which has a greater carcinogenic effect in the younger age group [4]. The distribution of thyroid cancer cases in the control series from former Western Europe, according to the age at diagnosis, increased progressively with the age; the majority (57%) of the patients being diagnosed after the age of 14 year (mean age at diagnosis was 14.6 ± 4.2) [4].

We have shared our similar experience[12] acquired since 1995 when, nine years after the April 1986 nuclear accident of Chernobyl, we were confronted with four similar cases of PTC (two with positive cervical lymph nodes, N1a and N1b) in youngsters aged 2 month to 9 years at the time of the Chernobyl accident and aged 10 to 18 years at the time of thyroid operation. We then reviewed our clinical experience with thyroid surgery and scrutinized our prospective data base in order to put these four young PTC patients into perspective, considering that since April 86 we had performed 1014 thyroidectomies in adults, among which 61 cases of thyroid cancers were detected (6.1 %). Despite the fact that childhood PTC is extremely rare (0.5 to 3 per million children per year) [4], during the same period, we performed thyroid operations in 18 children or adolescents among which the four PTC were found (22 %). Before April 1986, we did not operate on any childhood PTC and the percentage of PTC cancer found in adult patients undergoing thyroid surgery was 6%.

In the meantime, we questioned the Belgian Royal Institute of Meteorology (BRIM) [13] in order to obtain data about the possible atmospheric radioactive exposure of the Belgian population at the time of the Chernobyl accident. The information from the BRIM classified report was of utmost interest. Indeed, the mean value of natural atmospheric radioactivity is 3.2 $Bq.m^{-3}$ per year in Belgium. From 1-3 May 1986 (arrival of the first radioactive cloud from Chernobyl over Belgium), the mean daily value of radioactivity rose to over 70 $Bq.m^{-3}$ per day. By comparison, the mean daily value of radioactivity measured at ground level by the BRIM on 2nd and 3rd May, 1986 in Belgium was 20-fold higher than the mean daily values measured during and after a period of 110 important atmospheric nuclear bomb tests in 1961 and 1962 in the middle of the Cold War; and a hundred times the radioactivity measured in Belgium (700 $mBq.m^{-3}$ per day) on 11th and 12th October, 1957, after the nuclear accident in Winscale, UK (now called Sellafield). Based on these consecutive four cases of childhood PTC and the evidence of high radioactivity exposure in early May 1986, we thus raised the question of a possible relationship in Belgium between the occurrence of PTC and age of those children at the time of the Chernobyl nuclear plant accident, taking into account that the overall incidence of childhood PTC in Belarus and Ukraine rose significantly [4-8,14].

Furthermore, from January 2000 to January 2002, we operated on five other patients for papillary carcinoma follicular variant, who were respectively 8, 8, 10, 11 and 12-year-old at the time of the Chernobyl accident [15]. Apart from age, this initial cohort of nine patients also had the presence of psammoma bodies in two and elevated thyroglobulin autoantibodies (TgAb) in three [12,15]. We, therefore, pursued the prospective recording of all patients born before April 1986 operated for thyroid pathologies during the following three decades extending up to April 2015 [16].

In April 2011, in an effort to improve diagnostic and prognostic accuracy our Pathology department added several immunohistochemical (IHC) biomarkers [17,18] [cytokeratin 19 (CK 19), galectin-3 and HBME-1, a monoclonal antibody to an unknown microvillous surface antigen present on mesothelial cells]. to the classical cytological and histological investigations. IHC is able to recognize specific proteins on cytological or histological specimens [16]. All thyroid diagnostic immunomarkers share the ability to be expressed when the carcinoma appears. HBME1 is expressed in the majority of PTCs, showing diffuse strong staining. Similarly, CK19 consistently overexpressed in PTC, in both the classic and the follicular variant. Galectin-3, a

member of the B galactosil binding lectin family, for which normal functions include cell-cell regulation, growth, and appears to be a discriminating marker of well-differentiated follicular derived neoplasms [19-21]. The role of cell cycle regulatory protein, such as Cyclin D1, in the progression of thyroid cancer is another promising diagnostic factor [22]. In summary, all these antibodies can have a confirmatory role in distinguishing the follicular variants of PTC and follicular adenoma. For challenging encapsulated follicular lesions with questionable features of PTC, these antibodies can be helpful; their limitation perhaps suggesting the biologic ambiguity of the lesions [18-22].

In our experience [16] out of a total of 2349 patients having undergone thyroid surgery for all types of lesions during the three decades after Chernobyl and born before April 1986, 2164 were above 15 years of age at the time of the Chernobyl accident (*group A*) and 175 developed PTC (8.1%) compared to 36 PTC (19.5%) that occurred in 185 children under 15 years of age (*group B*) in April 1986 ($p<0.001$). Actually, we were expecting that with time this difference would have faded away due to the implementation of the more sophisticated diagnostic IHC allowing more accurate and earlier diagnosis of PTC, as well as less inter-observer variability in the evaluation of lesions [21] both in and between *groups A* and *B*. However, interestingly the gap of PTC incidence between groups A and B widened after the introduction in 2011 of IHC biomarkers. The use of these novel IHC markers did not reduce the difference in incidences between *groups A* and *B*, but instead widened it [16]. This fact constitutes an additional argument in favor of a long term follow up of children aged less than 15-year-old at the time of Chernobyl accident. It also contradicts a major study [4] that suggested the epidemic of radiation-induced thyroid cancer in children reached its peak in 1993, with a trend to a plateau in the following years. This study did not exclude, however, the possibility of a second peak occurring in the next few decades and having a longer latency period, similar to that observed after therapeutic external radiation to the head and neck [23-25].

The sources of information on the thyroid cancer risk after radiation exposure during childhood or adolescence after the nuclear plant accident of Chernobyl on 26 April 1986 [1-11], demonstrate that more than 70% of the thyroid dose of the population in the contaminated area was due to ^{131}I (half-life of 8 days), explaining the subsequent large increase of the thyroid cancer incidence in Belarus [26] and in Ukraine [27,28]. A case-control study including 107 thyroid cancer cases and two matched control groups of similar size indicated a strong relationship between thyroid cancer and radiation dose from the Chernobyl accident [29]. In another study [4], the excess absolute cancer risk per unit thyroid dose for the birth cohort 1971–1985 (i.e. age range similar to our *group B* of patients less than 15 years at the time of the Chernobyl accident) was found for the observation period of 4.6–9.6 years after the exposure to be 2.1 (95% CI 1.0–4.5) cases per 104 person-year Gy (ie. Gy for Gray, the unit of absorbed ionizing radiation dose in the International System of Units). In fact, those results were obtained from cohort studies of individuals whose thyroid ^{131}I activity was measured during the first two months after the accident. They demonstrate that the average thyroid doses to small children were about five times higher than the average doses to adults [4].

However, correlation does not imply causation. For instance, the dose evaluation remains an important issue that must be considered, especially for the evaluation of dose-response relationship after the more recent 2011 Fukushima accident. Indeed, the accumulated knowledge from the data on the atomic bomb survivors of Hiroshima and Nagasaki has, for a long time, been the basis of our understanding of the dose-response relationship for the risk of late health effects, including PTC. Since the risk estimates have been discussed mainly from the epidemiological data obtained from the atomic bomb survivors, who received high doses at extremely high-dose rate, these risk estimates may not be appropriately applied to populations receiving lower dose radiation exposure.

Such possible drawbacks, including also (a) long observation times necessary to gather enough cancer cases to achieve statistical power, and (b) uncertainties of individual thyroid radiation doses due to unknown thyroid mass at time of the Chernobyl accident, must be overcome before implying that ^{131}I radiation is the cause of PTC in people who were aged under 15 at time of the Chernobyl accident. We tried to overcome those drawbacks by prospectively recording the data from our surgical experience over the three decades since the Chernobyl accident in order to obtain relevant, valid and easily accessible data. Thanks to our study results, we can recommend that every practitioner facing a patient with a thyroid problem should check, as a simple first step, the date of birth. If she or he was aged less than 15-year-old, or even more significantly less than ten or five-year-old in April 1986, the physician must investigate thoroughly for the presence of thyroid cancer.

These drawbacks have also been be minimized in aggregate studies that decrease asymptomatic bias provided the covariate sample size in each cohort is important. Two such aggregate studies [4,30] of the thyroid cancer incidence in the contaminated areas of Belarus and Ukraine demonstrated the large potential of such analyses to derive quantitative results on the thyroid cancer risk after ^{131}I exposures.

Immunomarkers technology

The diagnosis of PTC is based on nuclear features; however, identification of these features is inconsistent and controversial. Saxen et al [31] found inter-observer agreement for thyroid tumours to be only 58%. This inter-observer variation is particularly true for encapsulated follicular lesions with partial or incomplete features of PTC. Williams [21] proposed the

term well-differentiated tumours of *uncertain malignant potential* (UMP) for such lesions in which the cytological features are not severe enough to provide an unequivocal diagnosis of PTC. These tumours have been suggested as possible precursors to invasive PTC. However, this term has not been accepted universally as a diagnostic term, and uncertainty remains about the nature of these lesions and their relationship to PTC. In an attempt to resolve this diagnostic difficulty, many IHC markers have been evaluated for their potential in distinguishing PTC from other follicular lesions. Proposed markers of PTC include HBME-1, galectin-3, specific cytokeratins (CK) such as CK19 [17]. Only rarely are all three markers negative in PTC; this panel therefore provides an objective and reproducible tool for the analysis of difficult thyroid nodules particularly since the introduction of follicular variant of PTC [18]. Experts consider that a panel of these IHC markers is of value to distinguish PTC from other thyroid follicular lesion, and is also helpful in the diagnosis of the follicular variant PTC. According to our experience, this was the case for the definitive diagnosis of PTC in 18 out of 22 patients (82%) from group A, and 11 out of 14 PTC patients from group B (79%) since April 2011. In addition, one study demonstrated a significant overexpression of cyclin D1 in aggressive thyroid carcinoma compared with conventional papillary carcinoma [22]. In our experience, cyclin D1 has contributed to the diagnosis of PTC in four patients (two in group A and two in group B) [16].

In the last decades, thyroid cancer incidence has increased continuously all over the world as demonstrated by one recent epidemiological review [32]. Many experts believe that the increased incidence of thyroid cancer is due to the increased detection of small cancers in the preclinical stage due to more sensitive diagnostic procedures, as well as the addition of new IHC markers to the histological exam of surgical specimen. Thus, the difference of incidences of PTC between our *groups A and B* could have been expected to reduce with time [16]. This, however, was not the case, with a continuous increase of PTC incidence in group A (>15 year in 1986) over the three decades since the Chernobyl accident. Therefore, increased radiation exposure remains the most likely contributing factor for increased rates of PTC in patients aged less than 15 years in 1986 [1,16,33].

The differences between the radiation exposure to the atomic bomb of Hiroshima and the radiation exposure from fallout after the Chernobyl accident

The consequences of exposure to radiation fallout after Chernobyl cannot be extrapolated from atom bomb studies. We already mentioned that the dose-response relationships for the risk of late health effects, including PTC, are different. In addition, the type of radiation (gamma rays emitting photons, and neutrons in Hiroshima versus beta minus rays in which electrons are produced, and gamma rays in Chernobyl), dose rate and the dose distribution in tissues (whole body distribution after Hiroshima versus variable distribution depending on the types of isotopes after Chernobyl), all differ [33]. Furthermore, after Chernobyl, amounts of radioactivity were detected for months around the whole northern hemisphere and not only in the most exposed areas of Belarus, Ukraine and the Soviet Union in 1986 [33].

As a matter of comparison, the nuclear bomb, called *Little Boy*, dropped by the B-29 flying superfortress *Enola Gay* on August 6, 1945 on Hiroshima was a uranium-fueled bomb that held 140 pounds of uranium, and exploded nearly 2000 feet above the city. In contrast, it is estimated that about seven to ten tons of nuclear fuel were released as a result of the explosion of reactor number 4 of the Chernobyl power plant that melted down at ground level, releasing volatile radioisotopes for months. Most experts agree that the areas in the 30 kilometres Chernobyl exclusion zone are still very contaminated with radioactive isotopes like caesium-137 and strontium-90, and, therefore, are unsafe for human habitation. Yet neither Nagasaki nor Hiroshima still suffer these conditions. The difference is attributable to three factors: (a) the Chernobyl reactor had a far greater amount of nuclear fuel; (b) that was much more efficiently used in nuclear reactions; and (c) the whole mess exploded at ground level. *Little Boy* detonated in mid-air allowing an important amount of radioactive debris to be dispersed by the mushroom cloud rather than being drilled on and into the earth. Today, over 1.6 million people live in Hiroshima, yet the Chernobyl exclusion zone, a 30 square kilometres area surrounding the plant, remains relatively uninhabited.

A survey study published in 2014 [34] investigating 3087 Hiroshima and Nagasaki atomic bomb survivors, aged less than 10 years old at exposure, demonstrated 62 to 66 years after their exposure 47 cases (1.8%) of thyroid cancers.

What should have been done after the Chernobyl accident: the experience of Poland

Thirty years after the Chernobyl accident, and despite the 2011 Fukushima accident, the consequences of nuclear power plant accident to human health continue to be widely denied often without proper arguments. One Belgian retrospective study published in 2008, and based on hospital discharge data, dealt with the incidence of surgically removed thyroid carcinoma (some histological types being not radiation-induced cancers) in Belgium ten years after Chernobyl [35]. In addition to the poor validity of their retrospective study, the authors did not give a balanced picture of the atmospheric radioactive contamination in early May, 1986 as reported in the Belgian Royal Institute of Meteorology document [13, 36]. The main risk factor is the radiation dose to the thyroid; the Chernobyl accident is estimated to have released approximately 1.7×10^{18} Bq of ^{131}I in the atmosphere in the areas around Chernobyl [21], but also over the northern hemisphere [12,13,33,36]. Af-

ter the Chernobyl accident, the basic measures of protection and precaution were not taken at the level of the entire European continent, that was still divided by the *Iron Curtain*, such as early iodine supplementation for children (at the exception of Poland[37]), and effective long term follow-up of all youngsters in the aftermath of the nuclear accident. For the following three decades after Chernobyl, an effective and efficient public health recommendation might have been to insist lowering the threshold to investigate patients presenting with thyroid lesions, who were aged less than 15 years of age in April 1986. This has been our policy for the past three decades [12,15,16] which probably explains that the majority of cases were T1 – T2 and N0. As we mentioned, from May 1 to 3, 1986 (the arrival of the first nuclear clouds from Chernobyl over Belgium [13]), the mean daily value of radioactivity rose to over 70 $Bq.m^{-3}$ *per day*. By comparison, in Poland the initial detection of atmospheric radioactivity on April 27 and 28 was up to 504 $Bq.m^{-3}$ of ^{131}I, with 1.55 to 3.0 higher values in northeast Poland. [37]Furthermore, in Warsaw on April 28, 28% of the air radioactivity was present as short-lived (8 days) isotopes of ^{131}I. Because reliable information was not available from Russia, Polish health authorities based their decisions on a worst case scenario; therefore, all children under 16 years of age received prophylactic potassium iodide (KI). KI was well tolerated, as shown by the Polish experience of administering it to a large population after the Chernobyl accident (10.5 million children and 7 million adults) [37]. The incidence of medically significant, but mild reactions (skin rashes, headache, vomiting, mild gastrointestinal disorders) to KI was low (0.2%) [37] demonstrating that KI distribution at a population level was a safe response. However, treatment with KI should begin as soon as possible after exposure, and continued, if necessary, for the duration of the exposure. In April 1986, the late admission of the nuclear accident by the Soviet Union authorities delayed by at least 48-hour the KI distribution in Poland.

In March 2011, Japanese officials failed to take early the decision to hand out KI pills to thousands of people. A decision that could minimize risk of radiation-induced injury from the nuclear accident. The disclosure of this error by the Wall Street Journal on September 2, 2011 was one of the first evidences of government neglect of emergency procedures in the chaotic weeks after the nuclear disaster, in which an earthquake and tsunami damaged the Fukushima Daiichi nuclear plant [38].

Two explosions occurred in Chernobyl, the first due to steam and a second due to hydrogen. Both explosions expelled fission products and fuel elements to the exterior that were drilled into the soil, but also accumulated on the ground and in a cloud reaching to approximately 7000 m and centred at 4500 m. The Chernobyl nuclear plant was equipped with early generation reactor RBMK (*Reaktor Bolshoy Moshchnosti Kanalnyy*), actually an old class of graphite-moderated nuclear power reactor designed by the Soviet Union. The Chernobyl reactor lacked the secondary containment found in modern nuclear power plants. As a consequence, when the graphite core ignited, there was a second, more prolonged release over a 9- to 10-day period that peaked on May 6, 1986, and began to drop only on May 11. We hope that these aspects of the Chernobyl disaster have been taken into account by the Japanese health authorities faced in March 2011 with the Fukushima nuclear power plant accident. We have some doubts, however, as we did not hear in 2011 about an equivalent mass media mobilization, as in Poland in 1986, to announce the protective action of KI and to appeal for volunteers to assist in a nationwide distribution of KI pills, especially in small villages [38].

It is worth mentioning that in August 1997, the U.S. National Cancer Institute acknowledged radiation exposure to millions of children during above ground nuclear weapons tests in the early 1950s and 1960s during the cold war [39]. More specifically, in 1983, the U.S. Congress directed the Department of Health and Human Services to assess the potential exposure of the American people to ^{131}I, one of the radioactive elements also found in the fallout from aboveground nuclear tests. The media blitz that followed this report heightened interest and concern among the public about thyroid cancer. In January 1997, the American Association of Clinical Endocrinologists (AACE) published the "AACE Clinical Practice Guidelines for the Management of Thyroid Carcinoma", and conducted the "*Stick Your Neck Out, America*" campaign to assist patients in recognizing and detecting thyroid cancer.

The type and molecular pathology of the thyroid tumours is changing with increasing latency; long latency tumours in other organs could occur also in the future. Therefore, a comprehensive follow up must continue for the lifetime of those exposed. Whenever a physical examination is done, the physician must always examine the thyroid and neck area. If a nodule or protrusion is seen or felt, ultrasonography possibly completed by needle biopsy should be done. Although a thyroid scan, ultrasound, or blood test may also be required, the thyroid needle biopsy is the best test to determine if a nodule is benign or is cancerous and requires surgery. We made the same type of plea in our papers of -2001 [12] and 2002 [15] and suggested that a long term epidemiological survey be considered at a European level.

Overall increase of the incidence of thyroid cancer

Incidence of thyroid cancer is increasing, which is probably due to better screening, and more effective preoperative diagnostic techniques. Significant progress has been made due to the development of several IHC biomarkers to complement the cytological and histological investigations on surgical specimens. This is clearly demonstrated in our study [16] by the rising incidence of PTC, both in *group A* and in *group B*, since April 2011 corresponding to the routine implementation of the novel IHC biomarkers. However, the persisting significant difference in incidence between groups A and B during the

past three decades cannot be explained only by those considerations. Indeed, if radiation-exposed adults may also develop PTC, their risk remains lower than for radiation-exposed children.

Pregnancy at the time of the Chernobyl accident

Because the thyroid is extremely sensitive to radioiodine in early childhood, due in part to the small size of the gland, one might also expect the foetus to be vulnerable. Moreover, the proliferative activity of fetal thyroid cells is high compared to children or adults [40]. To date, however, information about thyroid cancer risks associated with *in utero* exposure to Chernobyl fallout is very limited. In 2000, an ultrasound screening study of Belarusian school children living within 150 km of the Chernobyl plant[41] examined rates of thyroid cancer among those exposed prenatally (n=2409) and those exposed before three years of age (n=9720), and found higher rates in the postnatally exposed group compared with the in utero exposed (0.32%, n=31 cases vs. 0.09%, n=1 case, respectively). More recent (2003–2006) screening studies of 2582 individuals in northern Ukraine who were in utero during the period of Chernobyl fallout [42,43] calculated the dose-response relationship for thyroid cancer using individually estimated foetal thyroid ^{131}I doses for each member of the cohort [43]. The Excess Relative Risk/Gy (ERR/Gy), based on seven prenatally exposed cases of thyroid cancer, was 11.9 (P=0.12), substantially higher but not significant nor statistically different from the ERR/Gy of 3.24 estimated for a group of children exposed at 1–5 years of age (n=13 cases, P=0.01). The studies in Ukraine [42,43] had a longer period of follow-up than the earlier study in Belarus [41] (approximately 20 years versus 14 years) and more accurate dosimetric data but, although suggestive, it is by no means conclusive. The breakdown of the thyroid doses as a function of the stage of pregnancy shows that the dose increases substantially with the stage of pregnancy [42,43]. The lowest thyroid doses were estimated for subjects whose estimated foetal ages were less than 90 days at the time of the accident. Thyroid dose estimates generally increased with the stage of development, but also depend upon individual circumstances reported by the mothers.

In our experience with three PTC out of six prenatally exposed children [16], one was related to a young girl whose estimated foetal age was 35 weeks on April 26, 1986. She was born on April 30, 1986 and operated on in 1998 for bilateral multiple microscopic PTC at the age of 12 years. She was referred after a CT scan (without contrast injection) performed for a neck injury revealed concentrically punctuate calcifications in the right thyroid lobe suggestive of psammoma bodies, which were confirmed by histology [12]. The two other cases were T1aN0 and T2N0 PTC operated at age 22 and 23 years, whose foetal age on April 26, 1986 were 4 and 8 weeks respectively.

Clearly the issue of *in utero radiation exposure* will require additional research to establish both its role in thyroid cancer aetiology and the relative radiosensitivity of the prenatal versus the postnatal thyroid gland. We hope that such long term, population-based, research is under way in the Fukushima area.

Breastfeeding at the time of the Chernobyl accident

Few data are available. The possibility of a mother passing contaminated milk to her infant through breastfeeding is real. Independent tests on nine breast milk samples collected on March 24 and March 30 in the Fukushima region found radioactive ^{131}I in four nursing mothers – all of them living far from the exclusion zone. In fact, lactating may be more susceptible to ionizing radiation, as breast tissue bio-accumulates iodine as part of the physiological process of its accumulation in breast milk. These levels of accumulated radioiodine in breast milk may also increase the risk of thyroid cancer in newborns [44-46]. Our patient born on April 30, 1986 with a foetal age of 35 weeks on April 1986, who developed multiple microscopic bilateral foci of PTC at age 12, was breastfed[16]. Powdered milk formula for infants might have been better. However, in April 1986, cow's milk radioactivity varied widely from day to day, but as expected, remained elevated long after contamination of the air had subsided [37]. Once more, Poland can serve as an example: powdered milk programme initiated on April 29[37] lasted until May 7, when cow's milk radioactivity values had progressively declined and was judged safe for human consumption. At the same time, restriction of leavy vegetables was recommended.

Meteorological aspects of the problem

The Belgian Royal Institute of Meteorology (BRIM) report [13,36] is straightforward in its conclusions about the increase of atmospheric and ground level radioactivity in Western and Eastern Europe in late April and early May, 1986. This important piece of meteorological information can be extrapolated to the entire continent. More specifically, the radioactive cloud reached Belgium on May1st, 1986. Some authors [35] have deliberately overlooked those clear facts by pretending that radioactivity caused by the Chernobyl accident in Belgium was negligible. Furthermore, they supported their statement by one reference related to a survey of the ^{137}Cs contamination in Belgium a decade after the Chernobyl accident [47]. Late effects of ^{137}Cs contamination has nothing to do with the massive early ^{131}I contamination that represented 80% of the isotopes found in air samples taken during the first two weeks after the nuclear accident [37], and that deposited on the ground, grass and sand in Western Europe during the spring of 1986. In addition, the radioactivity of ^{137}Cs is 1400 times less than ^{131}I, that can also be ingested via irradiated cow's milk according to an early survey made in the Fukushima prefecture after the Fukushima Daiichi nuclear power plant in March 2011 [48].

The tricky analogy between contamination by ^{131}Iodine and ^{137}Caesium

After the Fukushima accident the minimum detectable activities (MDAs) for ^{137}Cs were ≤ 3.5 Bq kg^{-1} for ages 0-1year, decreasing to ≤ 2 Bq kg^{-1} for ages 10-11 year. Including the ^{134}Cs contribution, these translate to a maximum effective dose of 16μSv year^{-1} even for new born babies, and therefore the internal exposure risks can be considered negligibly small [49]. In contrast to Chernobyl, although both accidents were in the same level 7 of the International Nuclear Event Scale, the majority of children residing in the town of Miharu regularly consumed local or home-grown rice and vegetables, while in the town of Minamisoma, the majority avoid tap water and produces from Fukushima prefecture. The data show, however, no correlation between consumption of locally produced food and water and the children's body burdens [49]. Those impressive Japanese data have been obtained thanks to the development in 2013 (two years after the nuclear power accident) of the BABYSCAN, a whole body counter (WBC) for small children. WBC units have been installed at three hospitals in Fukushima Prefecture. Between December, 2013 and March, 2015, 2702 children between the ages of 0 and 11 have been scanned, and none had detectable levels of radioactive caesium (half-life of ^{137}Cs is 30.17 years). However, the measurements were made 33 to 49 months after the accident, which, as a consequence, eliminates the BABYSCAN as an effective tool for evaluation of the contamination by ^{131}I, whose half-life is eight days.

Serum Thyroglobulin and Thyroglobulin Autoantibodies

Some authors recommend to measure serum thyroglobulin (Tg), as its increase can be related to the risk of developing tumour following radiation treatment of benign thyroid conditions (e.g. toxic adenoma) [50]. In a study of 172 children with cancer, including 47 who were treated with radiation, thyroglobulin measurements were useful in identifying thyroid tumours [51]. However, a validated absolute risk model for second primary thyroid cancer among 5-year survivors of childhood cancer having received radiation did not include serum thyroglobulin level as a risk factor [52].

It has also been hypothesized that the increased prevalence of thyroglobulin autoantibodies (TgAb) in thyroid cancers could be due to an enhanced presentation of thyroid tumour antigens to the immune system, although this point is controversial [53]. If Tg is a well-established tumour marker in the follow-up of these patients, it is important to underline that retention of TgAb positivity reflects persistent disease, whereas the loss of TgAb positivity suggests a cure [54].

In one study [55], lymphocytic infiltration of the thyroid with the pattern of focal thyroiditis (in most cases) and of diffuse chronic thyroiditis (in some) was found in 50% of the Belarus patients in whom these changes could specifically be assessed. In a similar percentage of larger numbers of patients, serum antibodies to peroxidase and (less frequently) to thyroglobulin were detected. These figures should be compared with the 20% frequency of lymphocytic infiltration and humoral thyroid autoimmunity found in other Western European series [4]. All together, these data suggest that thyroid autoimmune reactions may also be related to radiation exposure. This interpretation is in keeping with the observation of thyroid autoimmune phenomena in several survivors of the atomic bomb explosions in August 1945 [4,56], as well as in subjects exposed to radiation fallout from military nuclear testing in the Marshall Islands during the Cold war from 1946 to 1958, including the first U.S. hydrogen bomb tested in 1952 [57,58]. It is worth noting that in 1956, the United States Atomic Energy Commission regarded the Marshall Islands as "by far the most contaminated place in the world" [58].

It is likely that thyroid autoimmunity may be an additional and important consequence of the Chernobyl accident. Thus, this potential risk must also be taken into account for the long term follow-up of people living in the nuclear fallout areas around Fukushima.

Late follow up

Thirty years have passed since the Chernobyl accident led to exposure of millions of people in Europe. Studies of populations [46] exposed have provided significant new information on radiation risks, particularly in relation to thyroid tumours following exposure to iodine isotopes. Recent studies among Chernobyl liquidators [59] have also provided evidence of increases in the risk of leukaemia and other haematological malignancies and of cataracts, and suggestions of increases in the risk of cardiovascular diseases, following low doses and low dose rates of radiation. Further careful follow-up of these populations, and long-term support of life-span study cohorts, may continue to provide important information for the quantification of radiation risks and the protection of persons exposed to low doses of radiation [59].

In 2014, the results of the evaluation of internal radiation exposure in Iwaki city (in the east-southern part of Fukushima Prefecture just south of the nuclear power plant), using whole-body counter (WBC) seemed to confirmed that the committed effective dose in residents was sufficiently low and comparable to the public dose limit (<1 mSv) [60]. The investigators, while continuing to communicate the radiation health risks with residents, recommended to pursue the follow-up studies in order to avoid so-called "unnecessary chronic internal exposure and to reduce anxiety among the residents" [60]. However, another Fukushima Health Management survey published in 2015 [61] was less optimistic. The individual external doses were estimated by using digitized behaviour data and a computer program that included daily gamma ray dose maps drawn after the accident. The individual external doses of 421,394 residents for the first four months (excluding radiation workers) had a distribution as follows: 62% < 1mSv, 94% < 2mSv, 99% <

3mSv. If the arithmetic mean was only 0.8 mSv, the maximum for the individual external dose was nevertheless 25 mSv. Furthermore, the response rate to the self-administered questionnaire and the participation in the survey, that was not compulsory, was only 26%. Thus, there is room for discussion about the results in terms of population safety. In addition, for children, the highest four-month dose was within a range of 10-11 mSv for each group of ages 0-9 year and 10-19 year. Higher dose (> 15mSv) were seen mainly for persons with delayed moves from the evacuation areas after the accident [61].

In 2016, a large panel of scientists from the Radiation Medical Centre for the Fukushima Health Management Survey [62] has implemented large monitoring projects that include the basic survey of the local populations for the estimation of external radiation doses received during the first 4 months after the accident, and four detailed surveys: thyroid ultrasound examination, comprehensive health check-up, mental health and lifestyle survey, and survey on pregnant women and nursing mothers, with the aim to prospectively take care of the health of all the residents of Fukushima prefecture for a long time. Last but not least, the panel also insisted on the fact that, among evacuees of the Fukushima accident, concern about radiation risk is associated with psychological stresses. Therefore, ongoing health risk management must also be focused on the difficult challenge of post-disaster recovery and resilience after a nuclear plant accident [62].

Nuclear Emergency Plan

Some progresses have been made in the field of measures that have to be taken in the event of a nuclear accident in several countries. In addition to international conventions concerning information exchange between countries (the International Atomic Energy Agency IAEA and the European Union), national nuclear emergency plans are defined by law. These emergency plans primarily concern the major nuclear plants. Transport incidents and radiological terrorism are also *theoretically* taken into account.

Distribution plans of iodine tablets in case of nuclear accident is another issue for which solutions are heterogeneous from one country to another, and that can vary with time in the same country. For instance, the Belgian National Study Centre for Nuclear Energy (SCK-CEN) mentioned in their contact letter of 2011 that it was decided within the context of the Belgian nuclear emergency plan to distribute stable iodine tablets (KI) around the major nuclear plants so they are quickly available if necessary. Since 2001, a so-called "Belgian policy on KI pre-distribution" has been designed for each family living in the *evacuation zone* (0 – 10 km around the nuclear power plant). A decentralised KI stockpiling in the pharmacies and communities was planned in the *sheltering zone* (10 – 20 km). In late 2015, the sheltering zone was increased to 100 km around the two Belgian nuclear power plants (seven reactors): one is located in the north-western and the other in the south-eastern part of Belgium. As a consequence, the new sheltering zones cover the entire Kingdom of Belgium and some parts of the bordering countries. In addition, several nuclear power plants of France are located close to the southern border of Belgium

The accident of Fukushima of March 2011 and the accident of April 1986 were of the same severity level. However, immediately after the Fukushima accident, and in contrast to the Chernobyl accident, appropriate countermeasures including evacuation, sheltering and control of food chain were implemented in a timely manner by the Japanese government according to official reports.[63,64] Nonetheless, this is somewhat in contradiction with earlier report [38]. Concerning the risk of thyroid cancer, it is well known that not only external but also internal exposure to radioactive iodine can increase it [1,65,66]. Once again, the most important modifier of radiation-induced thyroid cancer risk mentioned is age at exposure, and elevated risk faints among people exposed after the age of 20-30 [64]. In this sense, the measures taken in Fukushima are rather encouraging in terms of the strategy for prevention of radiation induced thyroid cancer. According to more precise estimated data from the local residents in Fukushima [67], the whole body absorbed doses were below 3mSv in general during the first four months after the accident. The most important point, however, is the thyroid dose evaluation in Fukushima suggesting the maximum not exceeding 35mSv in thyroid equivalent dose (between 0-15 mSv for 98% of children in Iwaki city, Kawamata town and Litate village in the Fukushima Prefecture) in a realistic manner[68] in comparison with the data obtained from the Chernobyl study (90% above 15mSv and 54% above 200mSv among the evacuees in Belarus) [59, 69].

At this stage, it is worth mentioning that in a Report of the Russian Scientific Committee on Radiological Protection [70], released in 2013, one can read: "It should be concluded that currently available preliminary radiation doses estimates show that after Fukushima nuclear power plant accident doses of the public resulting from this accident were significantly lower than those after the Chernobyl accident. Possibly, this is due both to differences in levels of radioactive environmental contamination as a result of these accidents and timely evacuation of people from the most contaminated areas around Fukushima nuclear power plant, as well as measures undertaken in Japan to prevent consumption of contaminated food [70]" .

Genetic profile of thyroid cancers after Chernobyl and Fukushima accidents

A recent molecular analytical study [71] showed that the genetic profile of Fukushima thyroid cancers was completely different from that of post-Chernobyl radiation-associated thyroid cancers in young patients.[71] Regarding radiation-induced thyroid carcinomas, post-Chernobyl paediatric PTCs had *RET/PTC* rearrangements detected in more than 50% [71-73]. *RET/PTC3* was found in 64-86% of the tumours with short latency (4-8 years after the exposure) [74], whereas tumours that developed after longer period of time had *RET/PTC1* predominantly.

By comparison, the Fukushima experience [71] demonstrates a high prevalence of *BRAF*^{V600E} mutation (63.2%) and low frequency of chromosomal rearrangements such as *RET/PTC* (10.3%) in young PTC cases found in Japan by the thyroid ultrasound screening program.

In the early period (2004-2005) after the discovery of the *BRAF* mutation in thyroid cancers, its prevalence in paediatrics PTCs was reported to be only 0-20% [75-78]. However, the studies analysed a limited number of cases. So far, the Japanese scientists cannot explain the discrepancy between results of molecular studies made in the post-Chernobyl era and more recently after the Fukushima accident. However, several explanations have been raised. First, the increase in *BRAF* mutation may be due to improved sensitivity of detection methods: use of PCR-restriction fragment length polymorphism and pyrosequencing. Secondly, the prevalence of the *BRAF*^{V600E} mutation depends on population and iodine intake [79]. In Japan, iodine intake is high and in Belarus iodine deficiency was frequent in children before 1986 [80]. Thirdly, the post-Fukushima thyroid ultrasound screening program was much more extensive, systematic and sensitive [81] than after the Chernobyl accident, allowing detection of thyroid tumours of smaller size and earlier in life. In fact, no high-resolution ultrasound apparatus was available early after the Chernobyl accident in Belarus. Consistent with this hypothesis, are the results of the Japanese survey demonstrating that thyroid tumours with the *BRAF*^{V600E} mutation were significantly smaller than *BRAF*^{V600E} –negative cases [71].

The most interesting feature of the Japanese survey is that it demonstrates, for the first time, the distribution of oncogenes in the young thyroid cancer cases discovered by large mass screening. However, the final conclusion of Japanese scientists is very cautious: "It is assumed that *BRAF*^{V600E} may not confer growth advantage on paediatric PTCs, and many of these cases grow slowly, suggesting that additional factors may be necessary to enhance tumour progression in paediatric PTCs [71]."

In January 2016, the members (mainly from Poland) of the GENRISK-T project (EU grant FP6 36495) [82] published the results of a study aimed at establishing whether individual genetic factors influence the risk of developing cancer of the thyroid after exposure to ionizing radiation. The study searched for global differences in molecular profiles in tumour tissue from patients who were either exposed to Chernobyl radiation as children (exposed to Chernobyl radiation, ECR) or were born after 1 January 1987 and therefore not exposed to radiation (not exposed to Chernobyl radiation, non-ECR). Both groups resided in the same areas so that potential confounding factors (e.g. environment) were minimized. Gene expression profiles with respect to intrinsic potential confounding factors including age at PTC diagnosis, mutational status and histological subtype of PTC were also investigated. An important feature of the investigated PTC patients was their young age in the ECR group (median 2.3 year, range 0.1-8.3) in April 1986; age at diagnosis of PTC: median 17.7, range 14.7 – 24.5. There were significant, but subtle, differences in gene expression profiles between non-ECR PTC and ECR PTC associated with previous low-dose radiation exposure at time of the Chernobyl accident. Ten genes (PPME1, HDAC11, SOCS7, CIC, THRA, ERBB2, PPP1R9A, HDGF, RAD51AP1, and CDK1) from the 19 investigated with quantitative RT-PCR were confirmed as being associated with radiation exposure in an independent, validation set of samples. The BRAF mutation exhibited independent effects on the PTC expression profile.

Some practical comments and recommendations

- The decision to operate on a thyroid nodule is generally based variably on clinical information, ultrasound exam, scintigraphy and fine-needle aspiration cytology which are able to detect most papillary carcinoma. However, if the patient's history reveals that she or he was aged less than 15 years of age at the time of the Chernobyl accident must serve as an additional important element for the decision to operate on; it is even more so if the patient was less than 10- or 5-year-old in April 1986.

- The great majority of post-Chernobyl tumours are papillary cancers. Those radiation-induced thyroid cancers are not more aggressive than sporadic cancers [83] and, so far, there is no radiation–specific molecular marker [84]. However, dietary iodine levels may have wide implications in radiation induced thyroid carcinogenesis, and iodine deficiency that was present in Belarus in 1986, could have increased incidence, reduced latency, and influenced tumour morphology and aggressiveness [79,80]. Therefore, dietary iodine status is important in thyroid cancer susceptibility after radioactive fallout exposure. These findings reinforce the need to prevent iodine deficiency generally [83].

- Continued surveillance of trends in cancer incidence, including thyroid cancer, is an important priority to evaluate the public health impact of the nuclear plant accidents and should continue until the complete burden of Chernobyl-related disease has been fully characterized. Much has still to be learned from the Chernobyl accident and from the more recent accident of Fukushima.

- Coordinators of National Cancer Registries all over the world should organise long-term assessment and follow-up of the thyroid status of citizens who were younger than 15 years in April 1986 to shed light on the existence – or not - of a persistent significant relationship between low-dose radiation after Chernobyl and PTC [84].

- Decision-makers' hubris ends in bad policy choice and encourages shoddy practice. Humility leads to strength and not to weakness. It is the highest form of self-respect to admit mistakes and to make amends for them. The Japanese authorities admitted that they did not concretely learn lessons from the Chernobyl disaster, and that their nuclear plants did not reach *A Level of Risk as Low as Reasonably Achievable (ALARA).* Among other things, they now recommend to establish a sys-

tem for long-term follow-up of all children at the time of nuclear power plant accident in order to overcome the uncertainty of low-dose effects of radiation, but also to monitor their physical and mental health [64].

- The determining factors of risk perception have been relatively well analysed in Fukushima, and these observations should offer valuable information for further studies. Certain Japanese scientists recognize that the nuclear disaster of Fukushima has changed pre-existing and emerging issues such as sense of value on human life and public risk awareness and perception.[64] There is clearly a new challenge to be met in order to establish a transparent radiation protection culture in Japan (and elsewhere), to better communicate on radiation risk, and to gain real social trust, as well as a new confidence in experts and politicians In other words, to meet the challenge of credibility.

- Those who accept the risk are not always those who will suffer from it. As far as nuclear power industry is concerned, it still suffers from two original sins: opacity and lies bound to its military origin. This has led to public fear and distrust illustrated by the evolution from the NIMBY syndrome (*"Not In My Backyard"*) to the BANANA syndrome (*"Build Absolutely Nothing Anywhere Near Anyone"*), which reflects the growing irrational (but understandable) opposition to technology in general and to nuclear energy in particular.

Conclusion

After the 1986 Chernobyl nuclear power plant accident, radiation exposure affected residents of regions well beyond Ukraine and Belarus. This has been clearly demonstrated by a 1990 meteorological report that did not receive wide diffusion until we happened to obtain it from the BRIM5 in the late nineties [13, 36].

More recently, after the Fukushima nuclear plant accident, some Japanese medical officers warned us that it will take a long time to extract a living lesson from Fukushima "since we are still in the middle of confusion and absurdity to develop and implement a trustable countermeasure that would cover the multi-dimensional aspects of a whole human life, somewhat similar to the proverbial six blind men trying to determine an elephant by touch [64]." This metaphor from Japan illustrates what the Belarusian writer Svetlana Alexievitch – 2015 Nobel Prize in Literature – described already in her 1997 book *Voices from Chernobyl* [85]. This living lesson, already 20-year-old, was never published by Belarusian state-owned publishing houses.

References

1. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res. 1995, 141(3): 259-277.

2. Baverstock K, Egloff B, Pinchera A, Ruchti C, Williams D. Thyroid cancer after Chernobyl. Nature. 1992, 359(6390): 21–22.

3. Zablotska LB, Ron E, Rozhko AV, Hatch M, Polyanskaya ON et al. Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chernobyl accident. Br J Cancer. 2011, 104(1): 181-187.

4. Pacini F, Vorontsova T, Demidchik EP, Molinaro E, Agate L et al. Post-Chernobyl thyroid carcinoma in Belarus Children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. J Clin Endocrinol. Metab. 1997, 82: 3563-3569.

5. Demidchik E, Kazakov VS, Astakhova LN, Okeanov AE, Demidchik YE. Thyroid cancer in children after the Chernobyl accident: clinical and epidemiological evaluation of 251 cases in the Republic of Belarus. In: Nagataki S., ed. Nagasaki Symposium, Chernobyl: Update and Future. 1994, Amsterdam: Excerpta Medica, Elsevier Press; 21-30.

6. Tronko N, Bogdanova T, Kommisarenko I, Epstein OV, Oliynyk V et al. Thyroid cancer in children and adolescents in Ukraine after the Chernobyl accident (1986-1995). In: Karaoglou A, Desmet G, Kelly GN, Menzel HG, eds. The Radiological Consequence of the Chernobyl Accident. 1996, ERU 16544 EN. Luxembourg: European Commission; 683-690.

7. Demidchik E, Drobyshevskaya IM, Cherstvoy ED et al. Thyroid cancer in children in Belarus. In: Karaoglou A, Desmet G, Kelly GN, Menzel HG, eds. The Radiological Consequence of the Chernobyl Accident. 1996, ERU 16544 EN. Luxembourg: European Commission; 677-682.

8. Sobolev B, Likhtarev I, Kairo I, Tronko N, Oleynik V et al. Radiation risk assessment of the thyroid cancer in Ukrainian children exposed due to Chernobyl. In: Karaoglou A, Desmet G, Kelly GN, Menzel HG, eds. The Radiological Consequence of the Chernobyl Accident. 1996, ERU 16544 EN. Luxembourg: European Commission; 741-748.

9. Tsyb AF, Parshkov EM, Shakhtarin VV, Stepanenko VF, Skvortsov VF, Chebotareva IV. Thyroid cancer in children and adolescents of Bryansk and Kaluga regions. In: Karaoglou A, Desmet G, Kelly GN, Menzel HG, eds. The Radiological Consequence of the Chernobyl Accident. 1996, ERU 16544 EN. Luxembourg: European Commission; 691-697.

10. Kazakov VS, Demidchik EP, Astakhova LN. Thyroid cancer after Chernobyl. Nature. 1992, 359(6390): 21.

11. Jacob P, Kenigsberg Y, Zvonova I, Goulko G, Buglova E et al. Childhood exposure due to the Chernobyl accident and thyroid cancer risk in contaminated areas of Belarus and Russia. Br J Cancer. 1999, 80(9): 1461-1469.

12. Blackburn DJ, Michel LA, Rosière A, Trigaux JP, Donckier JE. Occurrence of thyroid papillary carcinoma in young patients. A Chernobyl connection? J Pediatr Endocrinol Metab. 2001,

14(5): 503-506.

13. De Muer D, De Dycker E, Malcorps H, Trullemans L, Van Der Aowera L et al. Meteorological aspects of the Chernobyl nuclear accident : consequences for Belgium. Belgian Royal Institute of Meteorology, 1990. Brussels. Publication series N°.123 (ISSN 0020-255-X).

14. Schlumberger MJ. Papillary and Follicular Thyroid Carcinoma. N Engl J Med. 1998, 338: 297-306.

15. Michel L, Donckier J. Thyroid cancer 15 years after Chernobyl. Lancet. 2002, 359(9321):1947.

16. Michel L, Donckier J, Rosiere A, Fervaille C, Lemaire J et al. Post-Chernobyl incidence of papillary thyroid cancer among Belgian children less than 15 years of age in April 1986 : A 30-year surgical experience. Acta Chir Belg 2016, in press. DOI:1 0.1080/00015458.2016.1165528 Online since April 22, 2016

17. Cheung CC1, Ezzat S, Freeman JL, Rosen IB, Asa SL. Immunohistochemical diagnosis of papillary thyroid carcinoma. Mod Pathol. 2001, 14(4): 338-342.

18. Demellawy DE, Nasr A, Alowami S. Application of CD56, P63 and CK19 immunochemistry in the diagnosis of papillary carcinoma of the thyroid. Diagn Pathol. 2008, 3: 5-17.

19. Scognamiglio T, Hyjek E, Kao J, Chen YT. Diagnostic usefulness of HBME-1, Galectin-3, CK19, and CITED1 and evaluation of their expression in encapsulated lesions with questionable features of papillary thyroid carcinoma. Am J Clin Pathol. 2006, 126(5): 700-708.

20. Beesley MF, McLaren KM. Cytokeratin 19 and galectin-3 immunohistochemistry in the differential diagnosis of solidary thyroid nodules. Histopathology. 2002. 41(3): 236-243.

21. Williams ED. Guest Editorial: Two proposals regarding the terminology of thyroid tumors. Int J Surg Pathol. 2000, 8(3): 181-183.

22. Wang S, Lloyd RV, Hutzler MJ, Safran MS, Patwardhan NA et al. The role of cell cycle regulatory protein, Cyclin D1, in the progression of thyroid cancer. Mod Pathol. 2000, 13(8): 882-887.

23. Favus MJ, Schneider AB, Stachura ME, Arnold JE, Ryo UY et al. Thyroid cancer occurring as a late consequence of head-and-neck irradiation. Evaluation of 1056 pateints. N Engl J Med. 1976, 294(19): 1019-1025.

24. Refetoff S, Harrison J, Karanfilski BT, Kaplan EL, De Groot LJ et al. Continuing occurrence of thyroid carcinoma after irradiation to the neck in infancy and childhood. N Engl J Med. 1975, 292(4): 171-175.

25. DeGroot LJ, Paloyan E. Thyroid carcinoma and radiation: a Chicago endemic. JAMA. 1973, 255(5): 487-501.

26. Buglova EE, Kenigsberg JE, Sergeeva NV. Cancer risk estimation in Belarussian children due to thyroid irradiation as a consequence of the Chernobyl nuclear accident. Health Phys. 1996, 71(1): 45–49.

27. Likhtarev IA, Sobolev BG, Kairo IA, Tronko ND, Bogdanova TI et al. Thyroid cancer in the Ukraine. Nature. 1995, 375(6530): 365.

28. Sobolev B, Heidenreich WF, Kairo I, Jacob P, Goulko G et al. Thyroid cancer incidence in the Ukraine after the Chernobyl accident: comparison with spontaneous incidences. Radiat Environ Biophys. 1997, 36(3): 195–199.

29. Astakhova LN, Anspaugh LR, Beebe GW, Bouville A, Drozdovitch VV et al. Chernobyl-related thyroid cancer in children of Belarus: a case–control study. Radiat Res. 1998, 150: 349–356.

30. Jacob P, Goulko G, Heidenreich WF, Likhtarev I, Kairo I et al. Thyroid cancer risk to children calculated. Nature. 1998, 392(6671): 31–32.

31. Saxén E, Franssila K, Bjarnason O, Normann T, Ringertz N. Observer variation in histologic classification of thyroid cancer. Acta Pathol Microbiol Scand. 1978, 86A(6): 483-486.

32. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer : Update on epidemiology and risk factors. J Cancer Epidemiology. 2013.

33. Williams D. Radiation carcinogenesis:lessons from Chernobyl. Oncogene. 2009, 27 (Suppl 2): S9-S18.

34. Imaizumi M, Ohishi W, Nakashima E, Sera N, Neriishi K et al. Association of radiation dose with prevalence of thyroid nodules among atomic bomb survivors exposed in childhood (2007-2011). JAMA Intern Med. 2015, 175(2): 228-236.

35. Gilbert M, Thimus D, Malaise J, France FR, Camberlin C et al. Is there an increased incidence of surgically removed thyroid carcinoma in Belgium ten years after Chernobyl ? A study of hospital discharge data. Acta Chir Belg. 2008, 108(3): 318-322.

36. Michel L, Vandiepenbeeck M. Tchernobyl: Il faut tirer les leçons du passé. Carte blanche d'un chirurgien et d'un météorologue. Brussels, Le Soir, 27 avril 2011.

37. Nauman J, Wolff J. Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. Am J Med. 1993; 94(5): 524-532.

38. Hayashi Y. Japan officials failed to hand out radiation pills in quake's aftermath. The Wall Street Journal. September 29, 2011.

39. United States Senate Hearing 105-686– National Cancer Institute's Management of Radiation Studies, September 16, 1998.

40. Saad AG, Kumar S, Ron E, Lubin JH, Stanek J et al. Proliferative activity of human thyroid cells in various age groups and its correlation with the risk of thyroid cancer after radiation exposure. J Clin Endocrinol Metab. 2006, 91(7): 2672–2677.

41. Shibata Y, Yamashita S, Masyakin VB, Panasyuk GD, Nagataki S. 15 years after Chernobyl: new evidence of thyroid cancer. Lancet. 2001, 358(9297): 1965–1966.

42. Hatch M, Brenner A, Bogdanova T, Derevyanko A, Kuptsova N et al. A screening study of thyroid cancer and other thyroid diseases among individuals exposed in utero to iodine-131 from Chernobyl fallout. J Clin Endocrinol Metab. 2009, 94(3): 899–906.

43. Likhtarev IA, Kovgan L, Chepurny M, Ivanova O, Boyko Z et al. Estimation of the thyroid doses for Ukrainian children exposed in utero after the Chernobyl accident. Health Phys. 2011, 100(6): 583-593.

44. Bland EP, Docker MF, Crawford JS, Farr RF. Radioactive iodine uptake by thyroid of breast fed infants after maternal blood volume measurements. The Lancet. 1969, 2(7629): 1039 -1040.

45. Tazebay UH, Wapnir IL, Dohan O, Dohan O, Zuckier LS et al. The mammary gland iodide transporter is expressed during lactation and in breast cancer. Nat Med. 2000, 6(8): 871–878.

46. Hatch M, Ron E, Bouville A, Zablotska L, Howe G. The Chernobyl disaster: cancer following the accident at the Chernobyl nuclear power plant. Epidemiol Rev. 2005, 27: 56–66.

47. Uyttenhove J, Pommé S, Van Waeyenberge B, Hardeman F, Buysse J. Survey of the 137-Cs contamination in Belgium by in situ gamma spectrometry, a decade after the Chernobyl accident. Health Phys. 1997, 73(4): 644-646.

48. Tanaka K, Takahashi Y, Sakaguchi A, Umeo M, Hayakawa S et al. Vertical profiles of Iodine-131 and Cesium-137 in soils in Fukushima prefecture related to the Fukushima Daiichi power station accident. Geochemical Journal. 2012, 46: 73-76.

49. Hayano RS, Tsubokura M, Miyazaki M, Ozaki A, Shimada Y et al. Whole-body counter surveys of over 2700 babies and small children in and around Fukushima Prefecture 33 to 49 months after the Fukushima Daiichi NPP accident. Proceedings of the Japan Academy, Serie B91: Physical and Biological Sciences, July 2015.

50. Schneider AB, Bekerman C, Favus M, Frohman LA, Gonzalez C et al. Continuing occurrence of thyroid nodules after head and neck irradiation. Relation to plasma thyroglobulin concentration. Ann Intern Med. 1981, 94(2): 176-180.

51. Lando A, Holm K, Nysom K, Krogh Rasmussen A, Høier Madsen M et al. Serum thyroglobulin as a marker of thyroid neoplams after chilhood cancer. Acta Paediatr. 2003, 92(11): 1284-1290.

52. Kovalchik SA, Ronckers CM, Veiga LH, Sigurdson AJ, Inskip PD et al. Absolute risk prediction of second primary thyroid cancer among 5-year survivors of childhood cancer. J Clin Oncol. 2013, 31(1): 119-127.

53. Ericsson UB, Christensen SB, Thorell JI. A high prevalence of thyroglobulin autoantibodies in adults with and without thyroid disease as measured with a sensitive solid-phase immunosorbent radioassay. Clin Immunol Immunopathol. 1985, 37(2): 154-162.

54. Spencer CA, Takeuchi M, Kazarosyan M, Wang CC, Guttler RB et al. Serum thyroglobulin autoantibodies: prevalence, influence of serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab. 1998, 83(4): 1121-1127.

55. Pacini F, Mariotti S, Formica N, Elisei R, Anelli S et al. Thyroid autoantibodies in thyroid cancer : incidence and relation with tumour outcome. Acta Endocrinol (Copenh) 1988, 119(2): 373-379.

56. Nagataki S, Shibata Y, Inoue S, Yokoyama N, Izumi M. Thyroid disease among atomic bomb survivors in Nagasaki. JAMA 1994, 272(5): 364-370.

57. Conrad RA, Peglia DR, Fagin JA. Review of medical findings in a Marshallese population twenty-six years after accidental exposure to radiatioactive fallout. Brookhaven National Laboratory 51261, National Technical Information Service (NTIS), New York, January 1980.

58. Cooke S. In Mortal Hands: A Cautionary History of the Nuclear Age. Black Inc., 2009.

59. Cardis E, Hatch M. The Chernobyl accident – an epidemiological perspective. Clin Oncol. 2011, 23(4): 251-260.

60. Orita M, Hayashida N, Nukui H, Kudo T, Matsuda Ns et al. Internal radiation exposure dose in Iwaki City, Fukushima Prefecture after the accident at Fukushima Dai-ichi nuclear power plant. PLOS One. 2014, 9(12) : e114407.

61. Ishikawa T., Yasumura S., Ozasa K, Kobashi G, Yasuda Hiroshi et al. The Fukushima Health Management survey:estimation of external doses to residents in Fukushima prefecture. Scientific Reports. 2015, 5: 1-11.

62. Yamashita S. (on behalf of 30 collaborators). Radiation Medical Center for the Fukushima Health management Survey. Comprehensive health risk management after the Fukushima nuclear power plant accident. Clinical Oncology (Royal Coll Radiol) 2016.

63. Report of Japanese Government to IAEA Ministerial Conference on Nuclear Safety-Accident at TEPCO's Fukushima Nuclear Stations.

64. Yamashita S, Takamura N. Post-crisis efforts towards recovery and resilience after the Fukushima Daiichi nuclear power plant accident. Jpn J Clin Oncology. 2015, 45(8): 700-707.

65. Ron E. Ionizing radiation and cancer: evidence from epidemiology. Pediatr Radiol. 2002, 32(4): 232-237.

66. Ivanov VK, Kashcheev VV, Chekin SY. Radiation-epidemiological studies of thyroid cancer incidence in Russia after the Chernobyl accident; estimation of radiation risks, 1998-2008 follow-up period. Radiat Protect Dosim. 2012, 151: 489-499.

67. Nagataki S, Takamura N, Kamiya K, Akashi M. Measurements of individual radiation doses in residents living around the Fukushima nuclear power plant. Radiat Res. 2013, 180(5): 439-447.

68. Nagataki S, Takamura N. A review of the Fukushima nuclear power plant reactor accident: radiation effects on the thyroid and strategies for prevention. Curr Opinion Endocrinol Diabetes Obes. 2014, 21(5): 384-394.

69. Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y et al. Risk of thyroid cancer after exposure to 131-I in childhood. J Nat Cancer Inst. 2005, 97(10): 724-732.

70. Stepanenko VF. Fukushima-1 NPP Accident: Doses of Irradiation of Emergency Workers and Population. Report to Russian Scientifical Committee on Radiological Protection 2013, 4:1-10.

71. Mitsutake N, Fukushima T, Matsuse M, Rogounovitch T, SaenkoV et al. BRAFV600E mutation is highly prevalent in thyroid carcinomas in the young population in Fukushima: a different oncogenic profile from Chernobyl. Scientific Reports 2015, 5: article n°16976.

72. Ricarte-Filho JC, Li S, Garcia-Rendueles ME, Montero-Conde C, Voza F et al. Identification of kinase fusion oncogenes in post-Chernobyl radiation-induced thyroid cancers. J Clin Invest. 2013, 123(11): 1935-1944.

73. Hamatani K, Eguchi H, Ito R, Mukai M, Takahashi K et al. RET/PTC rearrangements preferentially occurred in papillary thyroid cancer among atomic bomb survivors exposed to high radiation dose. Cancer Res. 2008, 68(17): 7176–7182.

74. Nikiforov YE. Radiation-induced thyroid cancer: what we have learned from Chernobyl. Endocr Pathol. 2006, 17(4): 307–317.

75. Fenton CL, Lukes Y, Nicholson D, Dinauer CA, Francis GL. The RET/PTC mutations are common in sporadic papillary thyroid carcinoma of children and young adults. J Clin Endocrinol Metab. 2000, 85(3): 1170–1175.

76. Penko K, Livezey J, Fenton C, Patel A, Nicholson D et al. BRAF mutations are uncommon in papillary thyroid cancer of young patients. Thyroid. 2005, 15(4): 320–325.

77. Rosenbaum E, Hosler G, Zahurak M, Cohen Y, Sidransky D et al. Mutational activation of BRAF is not a major event in sporadic childhood papillary thyroid carcinoma. Mod Pathol. 2005, 18(7): 898–902.

78. Powell N, Jeremiah S, Morishita M, Dudley E, Bethel J et al. Frequency of BRAF T1796A mutation in papillary thyroid carcinoma relates to age of patient at diagnosis and not to radiation exposure. J Pathol. 2005, 205(5): 558–564.

79. Guan H1, Ji M, Bao R, Yu H, Wang Y et al. Association of high iodine intake with the T1799A BRAF mutation in papillary thyroid cancer. J Clin Endocrinol Metab. 2009, 94(5): 1612–1617.

80. Knobel M, Medeiros-Neto G. Relevance of iodine intake as a reputed predisposing factor for thyroid cancer. Arq Bras Endocrinol Metabol. 2007, 51(5): 701-712.

81. Hayashida N, Imaizumi M, Shimura H, Okubo N, Asari Y et al. Thyroid ultrasound findings in children from three Japanese prefectures: Aomori, Yamanashi and Nagasaki. PLOS One 2013; 8(12): 1-7.

82. Handkiewicz-Junak D, Swierniak M, Rusinek D, Oczko-Wojciechowska M, Dom G et al. Gene signature of the post-Chernobyl papillary thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2016, Jan 26.

83. Williams ED, Abrosimov A, Bogdanova T, Demidchik EP, Ito M et al. Morphologic characteristics of Chernobyl-related childhood papillary thyroid carcinomas are independent of radiation exposure but vary with iodine intake. Thyroid. 2008, 18(8): 847-852.

84. Williams D. Cancer after nuclear fallout: lessons from the Chernobyl accident. Nat Rev Cancer. 2002, 2(7): 543-549.

85. Alexievitch Svetlana. Voices from Chernobyl. Dalkey Archive Press, Chicago, 2005. First published in Russian as Tchernobylskaia. Molitva. by Editions Ostojie, 1997. Copyright © 1997 by Svetlana Alexievich. Translation © 2005 by Keith Gessen. ISBN 1-56478-401-0.