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ORIGINAL PAPER

Post-Chernobyl incidence of papillary thyroid cancer among Belgian children less than 15 years of age in April 1986: a 30-year surgical experience

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ABSTRACT

Objective: We raised the question of a possible relationship in Belgium between the occurrence of papillary thyroid carcinoma (PTC) and age of children (<15 years) at the time of the Chernobyl nuclear plant accident in April 1986.
Setting: Referral *university* centre for endocrine surgery.
Material and methods: Thirty-year prospective study of the experience of a surgical team with PTC since the Chernobyl accident, taken out of 2349 patients operated on for any thyroid lesions from April 1986 to April 2015, comparing the incidence of PTC by age groups.
Main outcome measurement: Comparison of PTC incidence in patients >15 years (group A) and children <15 years (group B) in April 1986.
Results: Out of a total of 2349 patients having undergone thyroid surgery for all types of lesions during 30 year after Chernobyl and born before April 1986, 2164 were >15 years of age at the time of the nuclear accident (*group A*) and 175 developed PTC (8.1%) compared to 36 PTC (19.5%) that occurred in 185 children <15 years of age (*group B*) in April 1986 ($p < 0.001$).
Conclusions: Radiation exposure affected residents of countries (including Belgium) well beyond Ukraine and Belarus. This was demonstrated by a 1990 meteorological report. Over 30 years, there has been a persistent higher incidence of PTC among Belgian children below the age of 15 years at the time of the Chernobyl accident. This relationship with age has even been strengthened by the implementation of more sophisticated immunohistochemical biomarkers diagnostic technology since April 2011.

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Chernobyl; Fukushima Childhood cancer; nuclear fallout; papillary thyroid carcinoma; radiation exposure; surgery

Introduction

Radiation exposure of the thyroid during childhood is the most clearly defined environmental 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.[1,2] After 1986, significant increases in pediatric PTC were reported in the geographical area that was most contaminated by releases of radioiodines from the damaged nuclear reactor of Chernobyl: the site of the Chernobyl plant in Ukraine, and the region most heavily exposed 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.

We here report our three decades long experience in Belgium with patients presenting PTC and having a potential history of childhood (<15 years of age) radiation exposure at the time of the Chernobyl disaster on 26 April 1986. The severity of the nuclear accident 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.

Material and Methods

In 1995, 9 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

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accident and aged 10–18 years at the time of thyroid operation.[3] 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 (0.5–3 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 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) [5] 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} $year^{-1}$ in Belgium. From 1–3 May 1986 (arrival of the first nuclear clouds from Chernobyl over Belgium), the mean daily value of radioactivity rose to over 70 Bq m^{-3} day^{-1}. By comparison, the mean daily value of radioactivity measured at ground level by the BRIM on 2 and 3 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} day^{-1}) on 11 and 12 October 1957, after the nuclear accident in Winscale, UK (now called Sellafield). Based on these consecutive four cases of childhood PTC and the proof and 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.[2,6]

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 years old at the time of the Chernobyl accident.[7] Apart from age, the similarities of patients in this initial series of nine youngsters lied in the presence of psammoma bodies in two patients and elevated thyroglobulin autoantibodies (TgAb) in three.[3,7] We, therefore, pursued the prospective recording of all patients born before April 1986 and operated on for thyroid pathologies during the following three decades extending up to April 2015. All patients from this survey were operated on by the same surgeon (L.A.M.) up to October 2012 and by two others (A.R. and C.B.) with the same academic background, in the same surgical service and environment from October 2012 to April 2015 using the same indications, identical surgical techniques and pathology facilities.

In April 2011, the service of Pathology in an effort to improve diagnostic accuracy and offer new prognostic criteria, added several immunohistochemical biomarkers [8,9] [cytokeratin 19 (CK 19), galectin-3 and HBME-1] to the classical cytological and histological investigations. Indeed, immunohistochemistry is an interesting technique able to recognize specific proteins on cytological or histological specimens. All thyroid diagnostic immunomarkers share the ability to be expressed when the carcinoma appears. HBME1 is a monoclonal antibody to an unknown microvillous surface antigen present on mesothelial cells. Its usefulness as a marker of thyroid malignancy in fine-needle aspiration and tissue specimens has been demonstrated in several studies, showing diffuse strong staining in the majority of PTCs. Similarly, CK19 has been shown to be 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 differentiation in some studies, seemed to be a discriminating marker of well-differentiated follicular derived neoplasms.[10,11] In summary, 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 are helpful in some cases; their limitation perhaps suggesting the biologic ambiguity of the lesions.[9,12]

This article concerns our 30-year surgical experience with PTC since the Chernobyl accident, taken out of a total of 2349 patients operated on for thyroid lesions during three main time spans: the period from 26 April 1986 to 31 December 1999 corresponding to our initial report about our experience with childhood thyroid cancer after the Chernobyl accident (*period i*); the period from 1 January 2000 to 31 March 2011 corresponding to the pursuit of our prospective study (*period ii*); the period from April 2011 up to April 2015

corresponding to the routine implementation of the immunohistochemical biomarkers technology added to the cytological and histological investigations (*period iii*).

Actually, we raised initially two simple issues:

(A) Is there an increased incidence of PTC in Belgian children who were under 15 years of age at the time of the Chernobyl accident in April 1986? The cutting age of 15 years was elected from the results of a pooled analysis of studies of radiation exposure [1] demonstrating that the risk of thyroid cancer was higher in patients exposed before age of 15 years. Risk decreased with increasing age at exposure, with little apparent risk with exposure after age of 20 years.

(B) If there is a relationship with age, has the rate of diagnosis been influenced and/or modified by the implementation of more sophisticated immunohistochemical biomarkers diagnostic technology since April 2011 (i.e., during *period iii*)?

Results

All patients from this study were born prior to the 26 April 1986. The patients born after this cutting date are not included in this survey. It is, however, worth mentioning that the incidence of PTC among them was 9%, which is above the incidence of 6% found in adult patients we operated on before April 1986.

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 >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 ($p < 0.001$) as illustrated in Figure 1. The difference between groups A and B persists throughout the three main time spans (i: 1986–1999; ii: 2000–2010; iii: 2011–2015) as illustrated in Figure 2, and this despite a steady increase of PTC incidence in group A between 1986 and 2015. Between periods 1986–1999 (i) and 2000–2010 (ii), there seemed to be a progressive decrease of the difference in incidences of PTC ($p = 0.082$). However, the combination of both groups demonstrated a persistent significant difference in PTC incidences (7.75% versus 15.60%; $p < 0.01$). Actually, we were even expecting that with time this difference would have faded away due to the implementation of the more sophisticated diagnostic technology of immunohistochemistry allowing more accurate and earlier diagnosis of PTC, as well as less interobserver variability in the evaluation of lesions [12] both in and between *groups A* and *B*. However, amazingly enough, the gap of PTC incidence between *groups A* and *B* increased in the third time span (iii: 2011–2015) despite a continuous increase of PTC incidences from 1986 to 2015. In fact, the introduction in 2011 of immunohistochemical biomarkers diagnostic technology (Figure 3) did not damp the difference

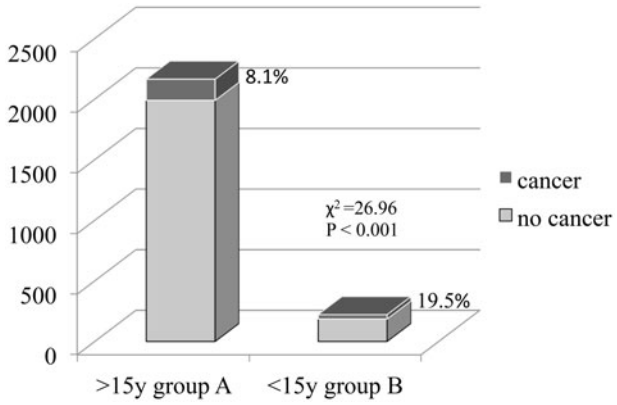

Figure 1. About 2349 thyroidectomies: 175 PTC (8.1%) in patients aged >15 years (*group A*) and 36 (19.5%) in patients aged <15 years (*group B*) at the time of Chernobyl.

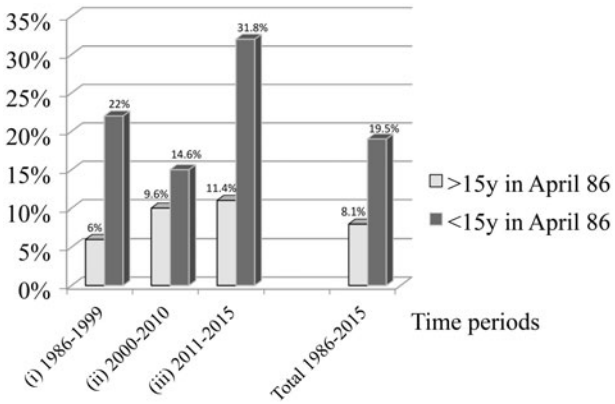

Figure 2. Percentage of PTC by *Time Periods*.

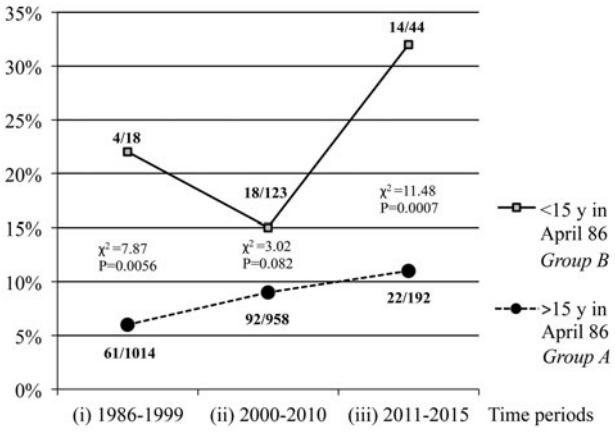

Figure 3. Evolution of the gap of PTC's incidence between patients aged more (*group A*) or less than 15 years (*group B*) in April 1986.

of incidences between groups A and B, but instead widened it.

The 36 patients of *group B* who subsequently presented a PTC (male/female ratio of 4/32) had a median age of 12 years (ranges: 1 month to 15 years) at the time of the Chernobyl accident. Their median age at the time of thyroid surgery was 33 (ranges: 11–40 years). The median duration of time between the Chernobyl accident and the timing of thyroid surgery was 19 years (ranges: 8–27 years). Age distribution of those 36 youngsters in April 1986 is illustrated in Figure 4.

All 36 cases are papillary variant follicular carcinoma of the thyroid. The TNM staging according to the American Joint Committee on Cancer (AJCC) is: 28 T1 (22 T1a and 6 T1b), 7 T2 and 1 T3. The nodes (N) categories are 31 N0, three N1a (5, 12, and 14 years of age at the time of the Chernobyl disaster) and two N1b (9 years of age at the time of Chernobyl). No patient presented with distant metastasis (M0). Indication for surgery was nodular thyroid in 32 patients, Grave's disease in two patients and voluminous multinodular goitre in two others who also presented Hashimoto thyroiditis. A close postoperative follow-up has been realized for all 36 patients. So far, the 36 patients are alive and free of PTC recurrence.

During the third period (iii) from April 2011 up to April 2015, 18 patients with PTC from group A (18/22 – 82%) and 11 from group B (11/14 – 79%) had their questionable features of PTC [12] also evaluated by immunohistochemical markers including CK19, galectin-3 and HBME1. Cycline D1 was added in four patients. When used, HBME1 was overexpressed in 15/18 (83%) for group A, and in 10/11 (90%) for group B; galectin-3 was overexpressed in 9/18 (50%) for group A, and in 6/18 (33%) for group B; CK19 was overexpressed in 15/18 (83%) for group A, and in 9/11 (82%) for group B. Combined overexpression of HBME1 and CK19 was present in 11/18 (61%) for group A, and in 9/11 (82%) for group B. Cycline D1, used in four patients, demonstrated higher expression in each case. In one T2N0M0 patient from group B, who did not overexpress HBME1, galectin-3 and CK19, cycline D1 demonstrated overexpression.[13]

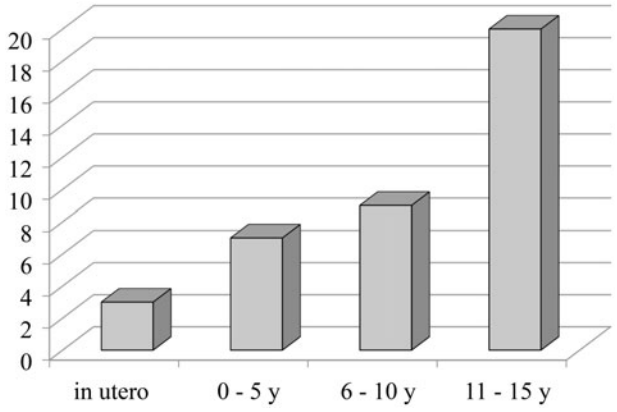

Figure 4. Age of the 36 youngsters at the time of the Chernobyl accident (plus three in utero) who developed PTC 8–27 years later.

We also recorded six patients who were *in utero* at the time of the Chernobyl accident. Their respective gestational ages were 4, 8, 12, 16, 24, and 36 weeks. Three of them presented with PTC at 12, 22, and 23 years of age with a corresponding gestational age at the time of the Chernobyl accident of 36, 4, and 8 weeks (Figure 4).

Serum Thyroglobulin (Tg; normal values between 0.2 and 70 ng/ml) and Thyroglobulin Autoantibodies (TgAb; normal value <10 U/ml) values were available pre- and post-operatively for the 36 PTC patients <15 years in 1986. Preop-Tg: median 63 ng/ml (range 0.3–2000), postop-Tg: median 2.9 ng/ml (range 0–45); preop-TgAb: 4 U/ml (range 0.3–2000); postop-TgAb median 6 U/ml (range 0.6–1035).

In summary, regarding the two main questions we raised in the method section – Is there an increased incidence of PTC in Belgian children who were under 15 years of age at the time of the Chernobyl accident in April 1986? If there is a relationship, has the rate of diagnosis been influenced and/or modified by the implementation of more sophisticated immunohistochemical biomarkers diagnostic technology since April 2011 (during period iii)? – the answer is clearly ***yes*** for both issues.

Discussion

The source 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,[1,2,6] demonstrated that >70% of the thyroid dose of the population in the contaminated area was due to ^{131}I (half-life of 8 days). In subsequent years, there was a large increase of the thyroid cancer incidence in Belarus [2,14] and in Ukraine.[15,16] A case–control study including 107 thyroid cancer cases and 2 matched control groups of similar size indicated a strong relationship between thyroid cancer and radiation dose from the Chernobyl accident.[17] In another study,[6] 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 <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 Chernobyl fallout 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 2 months after the accident. They demonstrate that the average thyroid doses of small children were about a factor of 5 higher than the average doses of adults.[6]

However, correlation does not imply causation. For instance, the dose evaluation remains an important issue that must be considered, more than ever, for the evaluation of dose–response relationship after the 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 moderate-to-high doses at extremely high-dose rate, these risk estimates may not be appropriate to be applied for populations receiving radiation dose at lower dose and low-dose rates after a nuclear power plant accident.

Such possible drawbacks, including also (a) long observation times necessary to gather enough cancer cases to achieve statistical power, and (b) large uncertainties of the individual thyroid radiation doses due to the unknown thyroid mass at the time of the Chernobyl accident, must be overcome before implying that ^{131}I radiation is the cause of PTC in people who were youngster at the time of the Chernobyl accident. We precisely tried to neutralize those drawbacks by prospectively recording our data from an homogenous surgical experience over the three decades since the Chernobyl accident in order to obtain useful information, that is to say relevant, valid and easily accessible. 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 birth date of the patient. If she or he was $<$15 year old, or even more significant $<$10 or 5 year old, in April 1986, the physician must think twice before trivializing the thyroid problem.

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 [6,18] 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 cancer risk after ^{131}I exposures.

Immunomarkers technology

In thyroid, the diagnosis of PTC is based on nuclear features; however, identification of these features is inconsistent and controversial. In one study, Saxen et al.[19] found inter-observer agreement for thyroid tumours to be only 58%, and similar findings have been documented repeatedly by additional studies. This inter-observer variation is particularly true for encapsulated follicular lesions with partial or incomplete features of PTC. Williams [12] proposed the term well-differentiated tumours of uncertain malignant potential (UMP) for such lesions in which the cytologic features are not developed enough to ensure an unequivocal diagnosis of PTC, and 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 common diagnostic difficulty, many immunohistochemical 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.[8] 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.[9] Experts consider that a panel of these immunohistochemical markers is of value in distinction of PTC from other thyroid follicular lesion, and is also helpful in the diagnosis of the follicular variant of PTC. This was clearly 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 (*period iii*). In addition, one study demonstrated a significant overexpression of cyclin D1 in aggressive thyroid carcinoma compared with conventional papillary carcinoma.[13] In our experience, cyclin D1 was contributive for the diagnosis of PTC in four patients (two in group A and two in group B).

In the last decades, thyroid cancer incidence has continuously increased all over the world. One recent epidemiological review [20] analyzed the possible reasons of this increase. Many experts

believe that the increased incidence of thyroid cancer is apparent, because of the increased detection of small cancers in the preclinical stage due to more sensitive diagnostic procedures, as well as the addition of immunohistochemical 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 fade away with time. This was not the case, however, despite the continuous increase of PTC incidence in group A (>15 years in 1986). Therefore, increased exposure to radiation remains most likely a contributing factor for PTC in patients <15 years of age in April 1986.[1]

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 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.[21] 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.[21] In fact, 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. For the first 2 days after the accident, the winds carried the radioactive dust over Finland and Sweden. On the third and fourth day, the wind shifted to bring it towards Poland, Czechoslovakia, Austria, and Northern Italy. It then shifted further westward and reached Belgium on 1 May 1986.[5]

As a matter of comparison, the nuclear bomb, called *Little Boy*, dropped by the B-29 flying superfortess *Enola Gay* on 6 August 1945 on Hiroshima was a uranium-fueled bomb that held 140 pounds of uranium, and exploded nearly 2000 feet above the city. The *Fat Man* bomb used in the bombing of Nagasaki on 9 August 1945 had a plutonium core. In contrast, it is estimated that ~7–10 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 radioisotopes for months. Most experts agree that the area in the 30 km Chernobyl exclusion zone are also terribly contaminated with radioactive isotopes like caesium-137, strontium-90 and plutonium, and, therefore, are unsafe for human habitation. Yet neither Nagasaki nor Hiroshima still suffers these conditions. The difference is attributable to three factors: (a) the Chernobyl reactor had a lot more nuclear fuel; (b) that was much more efficiently used in nuclear reactions; and (c) the whole mess exploded at ground level, while *Little Boy* and *Fat Man* detonated in mid-air allowing an important part of radioactive debris to be dispersed by the mushroom cloud rather than being drilled on and into earth. Today, over 1.6 million people live and seem to be thriving in Hiroshima, yet the Chernobyl exclusion zone, a 30 square kilometres area surrounding the plant, remains relatively uninhabited.

Actually, one other important point must not be skipped: the Chernobyl-type reactors were designed to produce plutonium for bombs while they generate electricity. They produced much more plutonium than Western European and U.S. reactors.

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 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 (several histological types being not radiation-induced cancers) in Belgium only 10 years after Chernobyl.[22] In addition to the poor validity of this type of retrospective study, the interpretation of the report of the Belgian Royal Institute of Meteorology [5] was one-sided, and not giving a balanced picture of the atmospheric radiation in early May 1986.[23] Furthermore, this study does not analyze the difference of PTC incidences between adults and children in 1986.

As far as the main risk factor is the radiation dose to the thyroid, one number constitutes, nevertheless, a definitive argument: the Chernobyl accident is estimated to have released in the

atmosphere $\sim 1.7 \times 10^{17}$ Bq of ^{131}I in areas around Chernobyl,[13] but also all over the northern hemisphere.[21] After the Chernobyl accident, the basic measures of protection and precaution have not been taken at the level of the entire European continent, that was still divided by the *Iron Curtain* in April 1986, such as early iodine supplementation for children (at the exception of Poland),[24] and effective follow up for decades of all youngsters in the aftermath of the nuclear accident. For the following three decades after Chernobyl, it would have been an effective and efficient public health recommendation to insist lowering the threshold of reaction and increasing the degree of vigilance of physicians faced with patients presenting with thyroid lesions, who were <15 years of age in April 1986. This has been our policy for the past three decades which explain probably that the majority of cases were T1–T2 and N0. As we mentioned in the method section of this article, from May 1 to 3 1986 (arrival of the first nuclear clouds from Chernobyl over Belgium), the mean daily value of radioactivity rose to over 70 Bq m^{-3} day^{-1}. By comparison, in Poland the initial detection of air radioactivity was made in April 27 and 28 and amounted to 504 Bq m^{-3} of ^{131}I, with 1.55–3.0 higher values in northeast Poland.[24] Furthermore, it was found in Warsaw on April 28, that 28% of the air radioactivity was present as short-lived (8 days) isotopes of iodine (^{131}I). Because reliable information was not available from the Soviet Union authorities, Polish health authorities based their decisions on the worst case scenario; therefore, all children under 16 years 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).[24] The incidence of medically significant, but not serious, reactions (skin rashes, headache, vomiting, mild gastrointestinal disorders) to KI was low (0.2%) [24] demonstrating that KI distribution at a population level was the correct and 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-h the KI distribution in Poland. By comparison, in March 2011, Japan officials failed to take early the decision to hand out KI pills to thousands of people. A decision that could have minimized radiation risks from the nuclear accident. This disclosure by the Wall Street Journal on 2 September 2011 was one of first evidence 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.[25]

As a matter of fact, 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 ~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 6 May 1986, and began to drop only on May 11. We hope that the risk of prolonged release of isotopes recorded during the Chernobyl disaster has been taken into account by the Japanese health authorities faced in March 2011 with the Fukushima nuclear 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.[25]

It is worth mentioning too that in August 1997, the 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.[26] More specifically, in 1983, the US 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 found also in the fallout from above ground 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 publications from 2001 [3] and 2002 [7] 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. As previously mentioned, significant progresses have been made more recently thanks to the development of several immunohistochemical biomarkers to complement the cytological and histological investigations. This is clearly demonstrated by the rising incidence of PTC, particularly in *group B*, during the third time span (iii) extending from April 2011 up to April 2015, and corresponding to the routine implementation of the immunohistochemical biomarkers technology added to the cytological and histological investigations. 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.

More specifically, the homogeneity of the recruitment of our patients in the French speaking part of Belgium and the standardized diagnostic and therapeutic practices adopted all along the past three decades for our study do away with the valid objections raised at the population level in the recent KCE (Belgian Health Care Knowledge Centre) report [27] regarding the variations in the epidemiology of thyroid cancer in Belgium, and the role of diagnostic and therapeutic strategies for thyroid diseases. The KCE report also demonstrates an age-specific incidence increase of thyroid cancer starting from the age of 15 years; the PTC being the most frequent histological type (73%). Considering the baseline figures from the KCE report which did not compare, as we did, the incidences of PTC in groups A and B, we are entitled to draw firmer conclusions on the potential impact of the Chernobyl accident on the incidence of PTC in children at the time of the nuclear fallout over Belgium.

Pregnancy at the time of the Chernobyl accident

Because the thyroid is extremely sensitive to radioiodines in early childhood, one might also expect the foetus to be vulnerable. Moreover, the proliferative activity of foetal thyroid cells is high compared with that in children or adults.[28] 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 [29] examined rates of thyroid cancer among those exposed prenatally ($n = 2409$) and those exposed before 3 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 versus 0.09%, $n = 1$ case, respectively). A more recent (2003–2006) screening study of 2582 individuals in northern Ukraine who were in utero during the period of Chernobyl fallout [30] calculated the dose–response relationship for thyroid cancer using individually estimated foetal thyroid ^{131}I doses for each member of the cohort.[31] 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 neither 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 study in Ukraine [30] had a longer period of follow-up than the earlier study in Belarus [29] (~20 years versus 14 years) and more accurate dosimetric data but, although suggestive, it is by no means conclusive. However, 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.[30,31] The lowest thyroid doses were estimated for subjects whose estimated foetal ages were <90 days (13 weeks) at the time of the accident. Thyroid dose estimates generally increased with the stage of development, but also depended upon individual circumstances reported by the mothers.

In our experience with three PTC out of six prenatally exposed children, one was related to a young girl whose estimated foetal age was 35 weeks on 26 April 1986. She was born on 30 April 1986 and operated on in 1998 for bilateral multiple microscopic PTC at the age of 12 years.

She was actually 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.[3] The two other cases were T1aN0 and T2N0 PTC operated at age 22 and 23 years, whose foetal age on 26 April 1986 were, respectively, 4 and 8 weeks.

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. Let us hope that such population-based research is under way effectively in the Fukushima area, and planned on a long-term basis.

Breastfeeding at the time of the Chernobyl accident

Few data are available. The possibility of a mother passing tainted 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.[32,33] Our patient born on 30 April 1986 with a foetal age of 35 weeks on April 1986, who developed multiple microscopic bilateral foci of PTC at the age of 12 years, was actually breastfed. Powdered milk formula for infants could 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.[23,24] Once more, Poland can serve as an example: after 7 May 1986, the cow's milk radioactivity values progressively declined and it was judged safe to terminate the powdered milk programme initiated on April 29.[25] At the same time, restriction of leafy vegetables was recommended.

Meteorological aspects of the problem in Belgium

The BRIM report [5,23] is straightforward in its conclusions about the important increase of atmospheric and ground level radioactivity starting in Belgium on 1 May 1986. Some authors [22] have clearly 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.[34] 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 2 weeks after the nuclear accident,[24] and that deposited on the ground, grass and in sandboxes where children were playing by sunny days in Western Europe during the spring of 1986. In addition, the radioactivity of ^{137}Cs is 1400 lesser 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 Daiichist nuclear power station in March 2011.[35]

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.[36] In a study of 172 children with cancer, including 47 who were treated with radiation, thyroglobulin measurements were useful in identifying thyroid tumours.[37] 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.[38]

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.[39] 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 can reflect persistent disease, whereas the loss of TgAb positivity suggests a cure.[40] Interestingly, TgAb was available pre- and post-operatively in all 36 PTC patients <15 years in April 1986. Six had elevated preoperative TgAb and normalized it after surgery; three other patients with associated Hashimoto autoimmune thyroiditis kept an elevated level of TgAb. Regarding Tg level, it was available in the 36 PTC patients <15 years in 1986, 21 patients had a preoperative high level of Tg which in 20 of them got back to normal or was

undetectable after radical surgery. The young girl who had an estimated foetal age of 35 weeks on 26 April 1986, and was operated on in 1998 for bilateral multiple microscopic PTC at the age of 12 years presented a high preoperative TgAb level (456 U/ml) that normalized after surgery.

Belgian Cancer Registry

The First Belgian Cancer Registry issued in 2011,[41] reporting the newest cancer incidence data for the year 2008 in Belgium, demonstrated that PTC showed a "large significant increase" between 1999 and 2008. Unfortunately, there is no general survey result in this registry regarding the possible impact of the Chernobyl accident on reported incidence of thyroid cancer in Belgium. Furthermore, thyroid cancer in children (age 0–14 years) being very rare, they were not included in the results that concern 5 year cancer incidence data for the Walloon and the Brussels Capital Regions, and 10 year cancer incidence data for the Flemish Region. Therefore, this registry is of no help to evaluate incidence of childhood thyroid cancer after Chernobyl inasmuch as children aged 0–3 years in April 1986 are not included in the figures. As a consequence of this lack of data, there is a major bias for an appropriate comparison with the incidence of PTC in older people at the time of the Chernobyl accident. The major registration inadequacies of the cancer registry, as far as PTC is concerned, during the past decades after the Chernobyl accident question its validity to bring appropriate answers to this much debated epidemiological issue. In the coming years, coordinators of the Registry should organize a long-term assessment and follow-up of the thyroid status of Belgian citizens who were younger than 15 years in April 1986 to shed light on the existence – or not – of a persistent causal relationship between age at exposure to radiation after Chernobyl and PTC.

Late follow up

Thirty years have passed since the Chernobyl accident led to exposure of millions of people in Europe. Studies of populations [33] 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 [42] 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 the establishment 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.[42]

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 Belgium. In addition to international conventions concerning information exchange between countries (the International Atomic Energy Agency IAEA and the European Union), the Belgian nuclear emergency plan is defined by law. This is a federal emergency plan which primarily concerns the major nuclear plants in or in the vicinity of Belgium, but transport incidents and radiological terrorism are also theoretically taken into account.

The national study centre for nuclear energy (SCK-CEN) mentions in his 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 predistribution" has been designed for each family living in the *evacuation zone* (0–10 km around the nuclear power plant). A decentralized KI stockpiling in the pharmacies and communities is planned in the *sheltering zone* (10–20 km). In late 2015, the sheltering zone has been 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.

In the wake of the recent controversy related to ageing Belgian nuclear plants, suddenly the Belgian Federal Agency for Nuclear Control recommended on 15 January 2016 to modify the emergency plan for nuclear accident. Among other recommendations, the agency proposed to extend the distribution KI pills to the entire population of Belgium should an accident occur, and the testing of the so-called "evacuation plan of the exclusion zones" around nuclear plants. Indeed, 930,000 people are living in the area 20 km radius around *Doel* nuclear

plant (close to Antwerp), and there are 500,000 residents in the 20 km radius around *Tihange* nuclear plant (between Namur and Liège).

Belgium authorities must rapidly draw clear lessons from the accident of Fukushima of March 2011, which had the same severity level 7 on the international nuclear event scale as the Chernobyl accident in April 1986. Indeed, immediately after the Fukushima 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.[43,44] However, this is somewhat in contradiction with earlier report.[25] Nevertheless, concerning the risk of thyroid cancer, it is well known that not only external but also internal exposure to radioactive iodine can increase it.[1,45,46] 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 years.[44] 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,[47] the whole body absorbed doses were <3 mSv in general during the first 4 months after the accident. The most important point, however, is the thyroid dose evaluation in Fukushima suggesting the maximum not exceeding 35 mSv in thyroid equivalent dose (between 0 and 15 mSv for 98% of children in Iwaki city, Kawamata town and Litate village in the Fukushima Prefecture) in a realistic manner [48] in comparison with the data obtained from the Chernobyl study (90% >15 mSv and 54% >200 mSv among the evacuees in Belarus).[42,49] Nevertheless, radioidine is only one of the many radioisotopes involved in the nuclear fallout after a serious nuclear power plant accident.

Some practical comments and recommendations

1. The decision to operate on a thyroid nodule is generally based variably on clinical information, ultrasound exam, scintigraphy and fine-needle aspiration cytology which is able to detect most papillary carcinoma. However, the fact that patient's history reveals that she or he was <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 <10 or 5 year old in April 1986.

2. The great majority of post-Chernobyl tumours are papillary cancers. Those radiation-induced thyroid cancers are not more aggressive than sporadic cancers [50] and, so far, there is no radiation–specific molecular marker.[51] 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. Therefore, dietary iodine status is important in thyroid cancer susceptibility after fallout exposure; these findings reinforce the need to prevent iodine deficiency generally.[50]

3. 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.

4. Coordinators of the Cancer Registry of Belgium should organize a long-term assessment and follow-up of the thyroid status of Belgian citizens who were younger than 15 years in April 1986 in order to shed light on the existence – or not – of a persistent significant relationship between low-dose radiation after Chernobyl and PTC.

5. Decision-makers' hubris ends often 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 L*evel of *R*isk as *L*ow as *R*easonably *A*chievable (ALARA principle). Among other things, they recommend to establish a system for long-term follow-up of all children at the time of nuclear power plant accident in order to not only overcome the uncertainty of low-dose effects of radiation, but also to keep their physical and mental health in calm and in peace for a long recovering time.[44]

6. Those who accept risks are not always those who will suffer from the consequences should an accident occur. As far as civil nuclear power industry is concerned, she still suffers from two original sins: opacity and lie 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. The term *Risk Society*, coined by Ulrich Beck,[52] is closely associated with the growing environmental concerns in modern societies; nuclear energy is part of it.

7. The demand for a zero defect and zero risk society is part of the managerial philosophy of the *Absolutes of Quality Management*. However, for nuclear power plants, this demand must be considered as a goal and not as a management program. Indeed, if the risk of nuclear accident is low, the potential consequences are tremendous at a population level and for a long time.

8. Some Japanese medical officers warn 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 multidimensional aspects of a whole human life, somewhat similar to the proverbial six blind men trying to determine an elephant by touch*".[44] This metaphor from Japan illustrates what the Belarusian writer Svetlana Alexievitch – 2015 Nobel Prize in Literature – described already in 1997 in her book [53] *Voices from Chernobyl*. This living lesson, already 20 year old, was never published by Belarusian state-owned publishing houses.

Conclusion

Exposure to radiations from the 1986 Chernobyl disaster has affected residents of countries (including Belgium) 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 BRIM [5] in the late nineties.[3,7]

Over three decades since April 1986, there has been a persistent higher incidence of PTC among Belgian children $<$15 years of in April 1986. This relationship with age has even been strengthened since the implementation of more sophisticated immunohistochemical diagnostic technology for the exam of surgical specimens since April 2011.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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