Cancer Science
Japanese Cancer Association JCA
Open Access

Review Article

Radiation signatures in childhood thyroid cancers after the Chernobyl accident: Possible roles of radiation in carcinogenesis

Keiji Suzuki, Norisato Mitsutake, Vladimir Saenko and Shunichi Yamashita

Department of Radiation Medical Sciences, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan

Key words
Chernobyl, chromosome rearrangement, radiation, signature, thyroid cancer

Correspondence
Keiji Suzuki, Department of Radiation Medical Sciences, Atomic Bomb Disease Institute, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan.
Tel: +81-95-819-7116; Fax: +81-95-819-7117;
E-mail: kzsuzuki@nagasaki-u.ac.jp

Funding information
Ministry of Education, Culture, Sports, Science and Technology, Japan.

Received September 27, 2014; Revised November 26, 2014; Accepted November 30, 2014

Cancer Sci **106** (2015) 127–133

doi: 10.1111/cas.12583

After the Tokyo Electric Power Company Fukushima Daiichi nuclear power plant accident, cancer risk from low-dose radiation exposure has been deeply concerning. The linear no-threshold model is applied for the purpose of radiation protection, but it is a model based on the concept that ionizing radiation induces stochastic oncogenic alterations in the target cells. As the elucidation of the mechanism of radiation-induced carcinogenesis is indispensable to justify the concept, studies aimed at the determination of molecular changes associated with thyroid cancers among children who suffered effects from the Chernobyl nuclear accident will be overviewed. We intend to discuss whether any radiation signatures are associated with radiation-induced childhood thyroid cancers.

It is generally recognized that radiation exposure takes part in cancer development in the human body. For example, increased risks in cancer mortality/incidence have been well described among atomic bomb survivors in Hiroshima and Nagasaki.[1] After the accident in the Chernobyl nuclear power plant (CNPP) in 1986, large amounts of radioactive materials were released into the environment, which caused excessive numbers of thyroid cancers among children living in contaminated areas neighboring the CNPP.[2,3] Clear dose-dependent induction of childhood thyroid cancers has proven that radiation exposure is the primary cause of thyroid cancer induction.[4–6] Thus, the Chernobyl childhood thyroid cancers have provided unequalled examples to unveil the molecular mechanisms of radiation-induced carcinogenesis.

After the Tokyo Electric Power Company Fukushima Daiichi nuclear power plant accident in 2011, people in Fukushima prefecture and across Japan expressed widespread concerns about health effects due to the release of radioactive materials.[7,8] Although the radiation doses to the public were not appreciably high, the worry is about the late effects of radiation, such as cancer induction.[9–11] A part of this anxiety, so-called radiation phobia, is ascribable to numerous uncertainties in our knowledge of the health effects from low-dose radiation exposure. As we have insufficient scientific evidence to depict the effects of low-dose exposure to radiation, current radiation protection policy has adopted the hypothesis called the linear no-threshold (LNT) model. It assumes that even a very low dose of radiation brings about non-zero risk of cancer induction. Although the LNT model has been evaluated for many years, there is still uncertainty about the linear relationship of low-dose exposure, such as to doses below 100 mSv.[11] One of the reasons for this uncertainty is insufficient mechanistic evidence available from epidemiological studies, so that the applicability of the LNT model to low-dose radiation exposure has not been fully evaluated. Moreover, the LNT model has been challenged by recent experimental observations, including non-targeted effects, which cast some doubts on the linearity of the dose–effect relationship, especially in the low-dose range.

An even more complicated issue is the applicability of the LNT model to life-long exposure to low-dose radiation at a low-dose rate. Although the dose and dose-rate effectiveness factor is used in current radiation protection guidelines, the linear concept is based on the assumption that stochastic radiation-induced oncogenic mutations persist in the target stem cells in tissues/organs. However, recent advances in stem cell biology have suggested that the integrity of stem cells is protected by multiple mechanisms, such as efficient DNA repair, stem cell competition, and tissue turnover. Thus, there is an urgent need to reconcile the recent observations that challenge

the persistence of stochastic oncogenic events in tissues and organs.[12] Moreover, through these findings, we have recognized the immediate need of extensive reconsideration of the theoretical basis of radiation-induced carcinogenesis in order to ascertain whether recent scientific observations sufficiently support the current carcinogenesis model, in which radiation-induced oncogenic mutations are involved in cancer development.

Childhood Thyroid Cancer after the Chernobyl Accident

After the accident at the CNPP on April 26, 1986, large amounts of radioactive materials were released, which lead to radiation exposure in the residents of affected areas.[2,3] Particularly, the fallout of radioactive iodine caused notable internal exposures in children through ingestion of contaminated milk and foodstuffs, which resulted in significant numbers of childhood thyroid cancer – one the of main health effects of the accident.[13,14] Four to 5 years after the accident, excessive cases of childhood thyroid cancers started to be reported. The increases in thyroid cancer were particularly profound among children aged between 0 and 4 years, whereas no such increase was observed in adults. Between 1991 and 2005, 5127 cases of thyroid cancer were reported among children under the age of 14 years in 1986, while 6848 cases were diagnosed in individuals exposed at when aged under 18 years.[3] Amongst children born after 1986, the incidence rate of thyroid cancer significantly declined almost to the background level, indicating that the considerable increase in thyroid cancers in childhood was due to the internal exposure to radioactive iodine.[6,15–18]

The most prevalent types of thyroid carcinomas are papillary thyroid carcinomas (PTC) and follicular thyroid carcinomas; the former is quite common in children and adults.[19] Almost all of the childhood thyroid carcinomas, including the earliest cases, were PTCs, in which the risk of cancer-related death is small.[20,21] While some increase in follicular thyroid carcinomas was observed over time, approximately 95% or more of the cases were PTC in most years. In earlier cases, nearly all PTCs were of the solid subtype, which was the unique characteristic observed after the Chernobyl accident.[21] Subsequently, the proportion shifted to the classic subtype, which is less aggressive and metastatic, and is the common subtype in sporadic childhood PTC.[19–21]

Iodine deficiency is a critical factor affecting the incidence of childhood thyroid cancer, as it promotes the intake of radioactive iodine and increases the size of the thyroid gland, and internal exposure to radiation from ^{131}I is apparently a well-established risk factor for thyroid cancer.[15–20,22,23] A large case–control study of Belarusian and Russian children showed a strong dose-dependent induction of thyroid carcinomas, and the risk seems to increase linearly with the dose.[15] Recent analysis of thyroid cancer prevalence in the Belarusian and the Ukrainian cohorts also estimated a linear dose–response relationship.[4,6] Thus, it is quite evident that radiation exposure is the causal factor associated with childhood thyroid cancer.

Another type of childhood cancer related to radiation exposure is childhood leukemia, which is well described in A-bomb survivors.[1] Unexpectedly, there was no increase in childhood leukemia after the Chernobyl accident, indicating that, in contrast to the internal exposure to radioactive iodine, external radiation exposure had negligible effects in terms of cancer induction. It has been reported that the risk of childhood leukemia in A-bomb survivors showed a linear–quadratic dose–response,[24] whereas the incidence of childhood thyroid cancer increased linearly with the dose. Although the difference has not yet been fully elucidated, the dose–response relationship of childhood thyroid carcinoma resembles that of other solid cancers observed in A-bomb survivors.[1]

As spontaneous childhood thyroid cancer in the areas surrounding the CNPP was quite rare, in general, most cases diagnosed after the Chernobyl accident could be attributable to radiation exposure. Therefore, these cases were expected to provide unique opportunities to demonstrate the existence of stochastic radiation signatures associated with malignant conversion of thyroid follicular cells.

Oncogenic Rearrangements in Childhood Thyroid Cancer after the Chernobyl Accident

After the Chernobyl accident, the highest risk for radiation-induced thyroid cancer was observed among children exposed at the age of 0–4 years. Early childhood thyroid cancer cases showed significantly higher prevalence of rearrangements between the rearranged during transfection (*RET*) gene and the *PTC3* gene (*RET/PTC3* rearrangement).[25–27] The *RET/PTC1* as well as *RET/PTC2* rearrangements were also reported.[27] It is well established that *RET/PTC1* gene rearrangement is the most prevailing genetic alteration in childhood PTCs after the Chernobyl accident overall.[19,20,28,29]

Fusions of the *RET* proto-oncogene with several partner genes, have been collectively designated the *PTC* genes, have been described (Table 1).[30] The *RET* gene encodes a transmembrane receptor tyrosine kinase. The binding of the ligands stimulates receptor dimerization, the critical step for activation of tyrosine kinase activity.[31,32] The fusion partner proteins are commonly expressed in thyroid follicular cells and possess coiled-coil domains that enable homodimerization of the fusion RET/PTC proteins (Fig. 1). As a result, RET/PTC proteins constitutively activate the MAPK pathway without any ligand binding (Fig. 2).[28,33–36]

Other types of rearrangements identified in childhood thyroid cancer related to the Chernobyl accident include juxtaposition of the A kinase anchor protein 9 (*AKAP9*) gene and v-*raf* viral oncogene homolog B1 (*BRAF*), designated *AKAP9-BRAF*,[37,38] rearrangement between translocated protein region (*TPR*) and the neurotrophic tyrosine kinase receptor type 1 (*NTRK1*) gene (*TPR–NTRK1*),[38] rearrangement between the *ETS* variant 6 (*ETV6*) gene and the *NTRK3* gene (*ETV6–NTRK3*),[38,39] rearrangement between the acylglycerol kinase (*AGK*) gene and the *BRAF* gene (*AGK–BRAF*),[38] rearrangement between the cAMP-responsive element binding protein 3-like 2 (*CREB3L2*) gene and the peroxisome proliferator-activated receptor γ (*PPARγ*) gene (*CREB3L2–PPARγ*),[38] and rearrangement between the paired box 8 (*PAX8*) gene and the *PPARγ* gene (*Pax8–PPARγ*) (Table 1).[38,40]

The *RET/PTC1* and *RET/PTC3* rearrangements are created through the paracentric (intrachromosomal) inversion within chromosome 10, where the *RET*, *CCDC6*, and *NCOA4* genes are assigned (Fig. 1).[34–36] Other *RET/PTC* rearrangements arise from interchromosomal translocations. Theoretically, at least two independent DNA double-strand breaks are necessary to produce a rearrangement. Therefore, these observations have logically brought about the hypothesis that radiation exposure from internal ^{131}I causes DNA double-strand breaks, resulting in oncogenic genome rearrangements after illegitimate recombination.[28] Notable association between radiation

Table 1. Oncogenic rearrangements in childhood thyroid cancers related to the Chernobyl accident

Oncogenes	Rearrangement partners	Chromosome locations	Type of rearrangements
RET rearrangements			
RET		10q11.2	
RET/PTC1	*CCDC6* (also *H4*)	10q21	Paracentric inversion
RET/PTC2	*PRKAR1A*	17q24.2	Interchromosomal translocation
RET/PTC3	*NCOA4* (also *Ele1*)	10q11.2	Paracentric inversion
RET/PTC4	*NCOA4* (also *Ele1*)	10q11.2	Paracentric inversion
RET/PTC5	*GOLGA5* (also *RFG5*)	14q32.12	Interchromosomal translocation
RET/PTC6	*TRIM24*	7q32-q34	Interchromosomal translocation
RET/PTC7	*TRIM33* (also *RFG7*)	1p13.1	Interchromosomal translocation
RET/PTC8	*KTN1*	14q22.1	Interchromosomal translocation
RET/PTC9	*RFG9* (also *MBD1*)	18q21	Interchromosomal translocation
BRAF rearrangements			
BRAF		7q34	
AKAP9/BRAF	*AKAP9*	7q21-q22	Paracentric inversion
AGK/BRAF	*AGK*	7q34	Paracentric inversion
NTRK rearrangements			
NTRK1		1q21-q22	
NTRK3		15q25	
TPR/NTRK1	*TPR*	1q25	Paracentric inversion
ETV6/NTRK3	*ETV6*	12p13	Interchromosomal translocation
PPARγ rearrangements			
PPARγ		3q25	
PAX8/PPARγ	*PAX8*	2q13	Interchromosomal translocation
CREB3L2/PPARγ	*CREB3L2*	7q34	Interchromosomal translocation

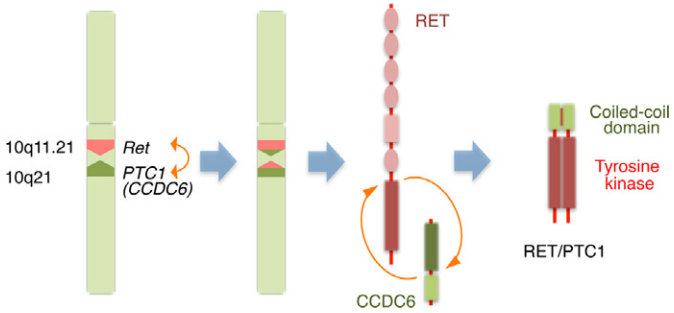

Fig. 1. Schematic representation of *RET/PTC1* rearrangements. A paracentric inversion of chromosome 10 gives rise to a fusion gene between the tyrosine kinase domain of the *RET* gene and the amino terminal region of the *CCDC6* gene. The fusion protein is constitutively activated through the dimer formation mediated by the coiled-coil domain of the CCDC6 protein.

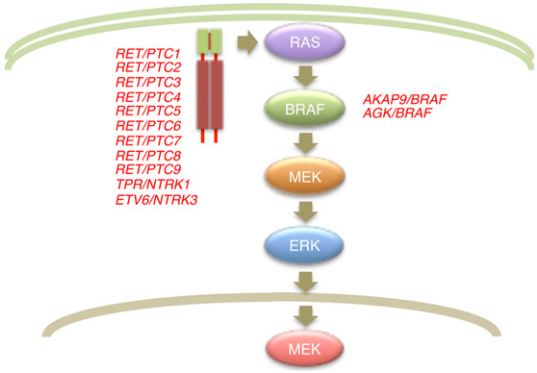

Fig. 2. Activation of the MAPK pathway in thyroid cancer. Most of the rearrangements identified in post-Chernobyl childhood thyroid cancers impair the physiological function of receptor tyrosine kinase activity, which results in constitutive activation of the MAPK pathway.

exposure and the induction of oncogenic rearrangement was demonstrated in experimental studies, in which radiation-induced *RET/PTC* rearrangements were confirmed in X-irradiated primary thyroid tissues transplanted into SCID mice.[41] However, one should be cautious about the conclusion, because the experiments used high-dose radiation exposure over 50 Gy. More recently, the generation of *RET/PTC* rearrangements have been identified in thyroid epithelial cells receiving much lower doses, although the frequency was quite low and dose-dependent induction was not clear.[42]

Although *in vitro* experiments seem to substantiate the hypothesis, *in vivo* studies have drawn a different picture. After the earlier studies, several independent groups have evaluated the prevalence of *RET/PTC* rearrangements in childhood thyroid cancer after the Chernobyl accident and compared the results with the frequency of *RET/PTC* rearrangements in sporadic childhood PTCs. The compiled data indicated that *RET/PTC* rearrangements were detectable to a comparable extent in both childhood thyroid cancers after the Chernobyl accident and sporadic childhood thyroid cancers.[43–45]

Extensive studies showed that the frequency of thyroid cancer with *RET/PTC* rearrangements decreases with age in sporadic cases, whereas those with the *BRAF* mutation becomes greater.[19] It is well established that these two genetic changes are mutually exclusive. Individuals born before the accident are now aged 28 years or older, and a recent report has suggested that the frequency of thyroid cancer harboring the *BRAF* mutation has tended to grow in the affected group, while *RET/PTC* rearrangements are still detectable.[46] This is another epidemiological observation indicating that molecular changes in thyroid cancer after the Chernobyl accident mirror those occurring spontaneously.

Thus, accumulating *in vivo* observations suggest that *RET/PTC* rearrangements observed in childhood thyroid cancer after the Chernobyl accident might not be the result of internal exposure to radiation from ^{131}I, but rather radiation exposure might play a non-targeted role in providing a tissue microenvironment, which eventually selects thyroid follicular cells with spontaneous *RET/PTC* rearrangement.

Copy Number Alteration as a Radiation Signature in Childhood Thyroid Cancer after the Chernobyl Accident

Radiation exposure is an efficient inducer of DNA double-strand breaks, therefore it is highly expected to cause gains or losses of DNA;[47] however, this notion was challenged by array comparative genomic hybridization analysis.[48] A variety of copy number alterations (CNAs) have been identified in childhood thyroid cancers after the Chernobyl accident, mostly gains of DNA, and these were compared with CNAs in sporadic cases, in which losses were more frequent than gains.[49–56] Consequently, it turned out to be clear that most studies have failed to demonstrate specific CNAs associated with radiation exposure, while one study, using an age- and ethnicity-matched cohort, described a unique gain of chromosome 7q11, which was absent in all unexposed cases.[57] A few genes are assigned to this chromosome band, although the overexpression of such gene products seems not to be the driver in childhood thyroid cancers. Thus, some copy number signatures might be associated with radiation-induced childhood thyroid cancers, however, their involvement in childhood thyroid carcinogenesis remains to be determined.

Gene Expression Signature

Previous studies have shown the differences in gene expression profiles between PTCs and normal thyroid tissues.[58–63] The strategy has been used to identify gene expression signatures that distinguish radiation-induced childhood thyroid cancers from sporadic cases. Several studies have been carried out and some of them reported gene expression changes unique to radiation-induced childhood PTCs, whereas others have failed to identify the signatures.[64–66] Importantly, the identified genes were very different between the studies, with few recurrent genes. More recently, gene expression profiles were compared in normal contralateral thyroid tissues obtained from exposed and unexposed children after the Chernobyl accident.[67] The study identified a gene expression signature, whose gene products are related to overall cell proliferation.

It should be taken into account that gene expression profiles could be affected by possible confounding factors such as age, ethnicity, and pathological features of the tumors, and these might have caused large discrepancies between the studies.[68] At present, it seems unlikely that common gene expression signatures could be associated with radiation-induced childhood thyroid cancers. As suggested by previous reports, the signatures might be dispensable for childhood thyroid carcinogenesis but rather they might reflect the results of radiation exposure.

Radiation Signatures and Possible Mechanisms of Radiation Carcinogenesis

It is generally accepted that cancer has arisen as a result of accumulation of oncogenic mutations. Mathematical considerations show that cancers, especially the solid cancers, show age-dependent increases in incidence roughly by the fifth power of age. This could be the most appropriate explanation why adulthood cancers make an appearance late in life. In clear contrast to adulthood cancers, childhood cancers are unique in their relatively short latency, suggesting that much fewer mutations are required. Some studies have indicated that mutations are acquired during fetal development,[69,70] but the principle of the difference in the number of mutations required for adulthood and childhood cancers remains to be determined.

Considering that childhood thyroid cancers started to manifest 4–5 years after the Chernobyl accident, it would be plausible to hypothesize that *RET/PTC* rearrangements were not directly caused by radiation exposure but might have already existed in the thyroid tissue. As discussed above, there has been supporting evidence that the frequency of *RET/PTC* rearrangements was not different between childhood thyroid cancers after the Chernobyl accident and sporadic cases. If radiation exposure is the direct inducer of *RET/PTC* rearrangements, the frequency should be significantly higher in radiation-related cases.

What, then, would be the role of radiation in thyroid carcinogenesis? One clue must be the inter-individual variations in response to radiation exposure after the Chernobyl accident, which could disclose the factors associated with the process of radiation-induced carcinogenesis. However, studies available so far have not identified genetic determinants that modify individual predisposition to radiation-induced childhood thyroid cancer. In particular, genome-wide association studies using adult sporadic thyroid cancers and Belarusian cases aged 0–18 years at the time of the accident pointed out that a common single nucleotide polymorphism marker, rs965513, located in the *FOXE1* vicinity at chromosome 9q22.33 showed a strong correlation with both sporadic and radiation-related thyroid cancer.[71] As FOXE1, also known as TTF-2, is a protein involved in the differentiation of thyroid gland, genetic predisposition to radiation-related thyroid cancer does not offer any signs for specific oncogenic alterations but suggests that

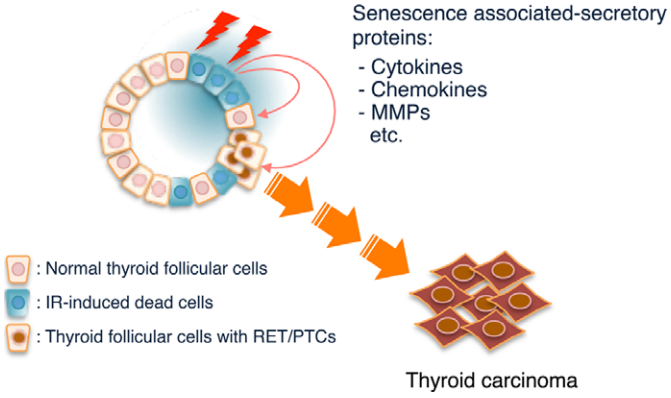

Fig. 3. Hypothetical model of radiation-induced thyroid carcinogenesis. Ionizing radiation (IR) executes senescence-like cell death in thyroid follicular cells, which promotes secretion of various factors including cytokines, chemokines, and matrix metalloproteinases (MMPs). Secretory proteins could stimulate inflammatory response and potentiate disruption of the tissues and the tissue microenvironment caused by radiation exposure. Our hypothetical model presumes that disruption and repair of the tissues and the tissue microenvironment creates a proliferative condition for thyroid follicular cells containing spontaneous oncogenic rearrangements, by which thyroid follicular cells could initiate the process towards thyroid cancers. PTC, papillary thyroid carcinoma; RET, rearranged during transfection.

anomalous tissue development could be targeted by radiation exposure.

Possible involvement of tissue disturbance in thyroid carcinogenesis has been discussed in the observations, in which chronic autoimmune thyroiditis, such as Hashimoto's thyroiditis, is sometimes accompanied by cancer.[72] Although the link is still debated, it seems likely that PTCs may develop if the cells with oncogenic mutations preexisted in the region with Hashimoto's thyroiditis. It should be noted that proliferative response was observed in Hashimoto's thyroiditis,[73] therefore, the disturbance of tissue homeostasis by chronic inflammation could create a condition for the cells harboring spontaneous *RET/PTC* rearrangement to undergo cell proliferation.[74]

In fact, some adverse effects of the Chernobyl accident on thyroid function have been reported in several studies, although the results are not always consistent due to the limited sample sizes and a lack of individual dose estimations. Earlier studies have shown the increased prevalence of thyroid autoimmune disorders among children exposed to the Chernobyl radioactive fallout 6–8 years after the accident, which was no more evident 12–14 years after the accident.[75,76] More recent studies have indicated that subclinical hypothyroidism still persisted among the individuals who were younger than 18 years of age on the day of the accident.[77] These observations imply that internal exposure to radioactive iodine may result in not a detrimental but notable disturbance in the thyroid gland of the affected children.

Recently, it has been recognized that ionizing radiation induces senescence-like cell death in thyroid follicular cells.[78] Moreover, senescence-like cell death promotes secretion of inflammatory cytokines,[79] so that it is tempting to speculate that radiation-induced tissue disruption could result in inflammatory circumstances that promote the initial stage of thyroid carcinogenesis (Fig. 3). Thus, taking all of this information into consideration, it is plausible to propose that a role of radiation in childhood thyroid cancers after the Chernobyl accident could be an introduction of tissue disturbance by inducing thyroid follicular cell death as well as introducing the secretory phenotype of dead cells (Fig. 3).

One should be cautious about this scenario, because many of the above speculations have to be experimentally proven. Also, the idea suggests that the stochastic induction of oncogenic mutations by radiation might not be the primary role of radiation exposure in childhood cancer development, rather, deterministic cell death could be involved. The risk of thyroid cancer incidence was estimated to increase linearly with radiation dose; however, these findings may cast doubt on the use of the LNT model, on which current risk estimation relies, especially at low doses. Thus, with further scientific investigations, we should reconsider the scientific significance of the LNT model especially for low-dose and low-dose-rate exposure. As such a condition currently exists in Fukushima prefecture, thorough studies will undoubtedly provide invaluable insights into this complication.

Conclusions

Internal exposure to radioactive iodine caused childhood papillary thyroid cancer after the Chernobyl accident. Molecular analyses have shown that *RET/PTC* rearrangements are the most prevailing oncogenic alteration in both radiation-induced and sporadic childhood thyroid cancer. Thyroid follicular cells might display selective growth, if the cells harbor spontaneous oncogenic rearrangements and if the tissue and tissue microenvironment are perturbed by cell death caused by ionizing radiation. The hypothetical model may cast some doubt on the current model of stochastic radiation carcinogenesis. Future studies will define the non-targeted role of radiation exposure, which should improve our understanding of multistep carcinogenesis induced by radiation exposure.

Acknowledgments

We thank Dr. Michiko Matsuse for critical reading of the manuscript. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Disclosure Statement

The authors have no conflict of interest.

References

1 Ozasa K, Shimizu Y, Suyama A *et al.* Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. *Radiat Res* 2012; **177**: 229–43.
2 United Nations Chernobyl Forum. Health effects of the Chernobyl accident and special health care programme. In: Bennett B, Repacholi M, Carr Z, eds. *World Health Organization Report of the UN Chernobyl Forum Expert Group "Health" (EGH)*. Geneva: World Health Organization, 2006.
3 United Nations. *Sources and Effects of Ionizing Radiation*. United Nations Scientific Committee on the Effects of Atomic Radiation. Report to the general assembly, with annexes C, D and E. New York, NY: United Nations, 2008; 2011.
4 Brenner AV, Tronko MD, Hatch M *et al.* I-131 dose response for incident thyroid cancers in Ukraine related to the Chernobyl accident. *Environ Health Perspect* 2011; **119**: 933–9.
5 Ivanov VK, Kascheev VV, Yu S *et al.* Radiation-epidemiological studies of thyroid cancer incidence in Russia after the Chernobyl accident (Estimation of radiation risks, 1991–2008 follow-up period). *Radiat Prot Dosimetry* 2012; **151**: 489–99.
6 Zablotska LB, Ron E, Rozhko AV *et al.* Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chornobyl accident. *Br J Cancer* 2011; **104**: 181–7.
7 *Health Risk Assessment from the Nuclear Accident after the 2011 Great East Japan Earthquake and Tsunami*. World Health Organization report. Geneva: World Health Organization, 2013.
8 United Nations. *Sources, Effects and Risks of Ionizing Radiation*. United Nations Scientific Committee on the Effects of Atomic Radiation, 2013 Report, with annexes A. New York, NY: United Nations, 2014.
9 Akiba S. Epidemiological studies of Fukushima residents exposed to ionising radiation from the Fukushima Daiichi Nuclear Power Plant prefecture–a preliminary review of current plans. *J Radiol Prot* 2012; **32**: 1–10.
10 Nagataki S, Takamura N, Kamiya K *et al.* Measurements of individual radiation doses in residents living around the Fukushima Nuclear Power Plant. *Radiat Res* 2013; **180**: 439–47.
11 Yamashita S, Tenth Warren K. Sinclair keynote address-The Fukushima Nuclear Power Plant accident and comprehensive health risk management. *Health Phys* 2014; **106**: 166–80.
12 Niwa O. Roles of stem cells in tissue turnover and radiation carcinogenesis. *Radiat Res* 2010; **174**: 833–9.
13 Saenko V, Ivanov V, Tsyb A *et al.* The Chernobyl accident and its consequences. *Clin Oncol (R Coll Radiol)* 2011; **23**: 234–43.
14 Demidchik YE, Saenko VA, Yamashita S. Childhood thyroid cancer in Belarus, Russia, and Ukraine after Chernobyl and at present. *Arq Bras Endocrinol Metabol* 2007; **51**: 748–62.
15 Cardis E, Kesminiene A, Ivanov V *et al.* Risk of thyroid cancer after exposure to ^{131}I in childhood. *J Natl Cancer Inst* 2005; **97**: 724–32.

16 Tronko MD, Howe GR, Bogdanova TI *et al.* A cohort study of thyroid cancer and other thyroid diseases after the chornobyl accident: thyroid cancer in Ukraine detected during first screening. *J Natl Cancer Inst* 2006; **98**: 897–903.
17 Ron E. Thyroid cancer incidence among people living in areas contaminated by radiation from the Chernobyl accident. *Health Phys* 2007; **93**: 502–11.
18 Likhtarov I, Kovgan L, Vavilov S *et al.* Post-Chernobyl thyroid cancers in Ukraine. Report 2: risk analysis. *Radiat Res* 2006; **166**: 375–86.
19 Yamashita S, Saenko V. Mechanisms of disease: molecular genetics of childhood thyroid cancers. *Nat Clin Pract Endocrinol Metab* 2007; **3**: 422–9.
20 Williams D. Radiation carcinogenesis: lessons from Chernobyl. *Oncogene* 2009; **27**: S9–18.
21 Tuttle RM, Vaisman F, Tronko MD. Clinical presentation and clinical outcomes in Chernobyl-related paediatric thyroid cancers: What do we know now? What can we expect in the future? *Clin Oncol (R Coll Radiol)* 2011; **23**: 268–75.
22 Gembicki M, Stozharov AN, Arinchin AN *et al.* Iodine deficiency in Belarusian children as a possible factor stimulating the irradiation of the thyroid gland during the Chernobyl catastrophe. *Environ Health Perspect* 1997; **61**: 1487–90.
23 Cardis E, Hatch M. The Chernobyl accident- an epidemiological perspective. *Clin Oncol (R Coll Radiol)* 2011; **23**: 251–60.
24 Hsu W-L, Preston D, Soda M *et al.* The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950–2001. *Radiat Res* 2013; **179**: 361–82.
25 Fugazzola L, Pilotti S, Pinchera A *et al.* Oncogenic rearrangements of the *RET* proto-oncogene in papillary thyroid carcinomas from children exposed to the Chernobyl nuclear accident. *Cancer Res* 1995; **55**: 5617–20.
26 Klugbauer S, Lengfelder E, Demidchik EP *et al.* High prevalence of RET rearrangement in thyroid tumors of children from Belarus after the Chernobyl reactor accident. *Oncogene* 1995; **11**: 2459–67.
27 Nikiforov YE, Rowland JM, Bove KE *et al.* Distinct pattern of *ret* oncogene rearrangements in morphological variants of radiation-induced and sporadic thyroid papillary carcinomas in children. *Cancer Res* 1997; **57**: 1690–4.
28 Nikiforov YE, Nikiforova MN. Molecular genetics and diagnosis of thyroid cancer. *Nat Rev Endocrinol* 2011; **7**: 569–80.
29 Santoro M, Carlomagno F. Oncogenic rearrangements driving ionizing radiation-associated human cancer. *J Clinic Invest* 2013; **11**: 4566–8.
30 Shaw AT, Hsu PP, Mark M *et al.* Tyrosine kinase gene rearrangements in epithelial malignancies. *Nat Rev Cancer* 2013; **13**: 772–87.
31 Kodama Y, Asai N, Kawai K *et al.* The RET proto-oncogene: a molecular therapeutic target in thyroid cancer. *Cancer Sci* 2005; **96**: 143–8.
32 Wang X. Structural studies of GDNF family ligands with their receptors-insights into ligand recognition and activation of receptor tyrosine kinase RET. *Biochim Biophys Acta* 2013; **1834**: 2205–12.
33 Zitzelsberger H, Bauer V, Thomas G *et al.* Molecular rearrangements in papillary thyroid carcinomas. *Clin Chim Acta* 2010; **411**: 301–8.
34 Menicali E, Moretti S, Voce P *et al.* Intracellular signal transduction and modification of the tumor microenvironment induced by RET/PTCs in papillary thyroid carcinoma. *Front Endocrinol* 2012; **3**: 1–23.
35 Santoro M, Carlomagno F. Central role of RET in thyroid cancer. *Cold Spring Harb Perspect Biol* 2013; **5**: 1–17.
36 Mulligan LM. RET revisited: expanding the oncogenic portfolio. *Nat Rev Cancer* 2014; **14**: 173–86.
37 Ciampi R, Knauf JA, Kerler R *et al.* Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAPK pathway activation in thyroid cancer. *J Clin Invest* 2005; **115**: 94–101.
38 Ricarte-Filho JC, Li S, Garcia-Rendueles MER *et al.* Identification of kinase fusion oncogenes in post-Chernobyl radiation-induced thyroid cancers. *J Clin Invest* 2013; **123**: 4935–44.
39 Leeman-Neill RJ, Kelly LM, Liu P *et al.* ETV6-NTRK3 is a common chromosomal rearrangement in radiation-associated thyroid cancer. *Cancer* 2014; **120**: 799–807.
40 Leeman-Neill RJ, Brenner AV, Little MP *et al.* RET/PTC and Pax8/PPARγ chromosomal rearrangements in post-Chernobyl thyroid cancer and their association with iodine-131 radiation dose and other characteristics. *Cancer* 2013; **119**: 1792–9.
41 Mizuno T, Iwamoto KS, Kyoizumi S *et al.* Preferential induction of RET /PTC rearrangement by X-ray irradiation. *Oncogene* 2000; **19**: 438–43.
42 Caudill CM, Zhu Z, Ciampi R *et al.* Dose-dependent generation of RET /PTC in human thyroid cells after in vitro exposure to γ-radiation: a model of carcinogenic chromosomal rearrangement induced by ionizing radiation. *J Clin Endocrinol Metab* 2005; **90**: 2364–9.
43 Fenton CL, Lukes Y, Nicholson D *et al.* The ret/ptc mutations are common in sporadic papillary thyroid carcinoma of children and young adults. *J Clin Endocrinol Metab* 2000; **85**: 1170–5.
44 Xing M. BRAF mutation in thyroid cancer. *Endocr Relat Cancer* 2005; **12**: 245–62.
45 Romei C, Elisei R. RET/PTC translocations and clinico-pathological features in human papillary thyroid carcinoma. *Front Endocrinol* 2012; **3**: Article 54, 1-8.
46 Tronko M, Bogdanova T, Voskoboynyl L *et al.* Radiation induced thyroid cancer: Fundamental and applied aspects. *Exp Oncol* 2010; **32**: 200–4.
47 Mullenders L, Atkinson M, Paretzke H *et al.* Assessing cancer risks of low-dose radiation. *Nat Rev Cancer* 2009; **9**: 596–604.
48 Zitzelsberger H, Unger K. DNA copy number alterations in radiation-induced thyroid cancer. *Clin Oncol (R Coll Radiol)* 2011; **23**: 289–96.
49 Hemmer S, Wasenius VM, Knuutila S *et al.* DNA copy number changes in thyroid carcinoma. *Am J Pathol* 1999; **154**: 1539–47.
50 Zitzelsberger H, Lehmann L, Hieber L *et al.* Cytogenetic changes in radiation-induced tumors of the thyroid. *Cancer Res* 1999; **59**: 135–40.
51 Richter H, Braselmann H, Hieber L *et al.* Chromosomal imbalances in post-Chernobyl thyroid tumors. *Thyroid* 2004; **14**: 1061–4.
52 Kimmel RR, Zhao LP, Nguyen D *et al.* Microarray comparative genomic hybridization reveals genome-wide patterns of DNA gains and losses in post-Chernobyl thyroid cancer. *Radiat Res* 2006; **166**: 519–31.
53 Finn S, Smyth P, O'Regan E *et al.* Low-level genomic instability is a feature of papillary thyroid carcinoma: an array comparative genomic hybridization study of laser capture microdissected papillary thyroid carcinoma tumors and clonal cell lines. *Arch Pathol Lab Med* 2007; **131**: 65–73.
54 Rodrigues R, Roque L, Espadinha C *et al.* Comparative genomic hybridization, BRAF, RAS, RET, and oligo-array analysis in aneuploid papillary thyroid carcinomas. *Oncol Rep* 2007; **18**: 917–26.
55 Unger K, Malisch E, Thomas G *et al.* Array CGH demonstrates characteristic aberration signatures in human papillary thyroid carcinomas governed by RET/PTC. *Oncogene* 2008; **27**: 4592–602.
56 Stein L, Rothschild J, Luce J *et al.* Copy number and gene expression alterations in radiation-induced papillary thyroid carcinoma from Chernobyl pediatric patients. *Thyroid* 2010; **20**: 475–87.
57 Hess J, Thomas G, Braselmann H *et al.* Gain of chromosome band 7q11 in papillary thyroid carcinomas of young patients is associated with exposure to low-dose irradiation. *Proc Natl Acad Sci USA* 2011; **108**: 9595–600.
58 Huang Y, Prasad M, Lemon WJ *et al.* Gene expression in papillary thyroid carcinoma reveals highly consistent profiles. *Proc Natl Acad Sci USA* 2001; **98**: 15044–9.
59 Chevillard S, Ugolin N, Vielh P *et al.* Gene expression profiling of differentiated thyroid neoplasms: diagnostic and clinical implications. *Clin Cancer Res* 2004; **10**: 6586–97.
60 Jarzab B, Wiench M, Fujarewicz K *et al.* Gene expression profile of papillary thyroid cancer: sources of variability and diagnostic implications. *Cancer Res* 2005; **65**: 1587–97.
61 Eszlinger M, Wiench M, Jarzab B *et al.* Meta- and reanalysis of gene expression profile of hot and cold nodules and papillary thyroid carcinoma for gene groups. *J Clin Endocrinol Metab* 2006; **91**: 1934–42.
62 Delys L, Detours V, Franc B *et al.* Gene expression and the biological phenotype of papillary thyroid carcinomas. *Oncogene* 2007; **26**: 7894–903.
63 Handkiewicz-Janak D, Czarniecka A, Jarzab B *et al.* Molecular prognostic markers in papillary and follicular thyroid cancer: current status and future directions. *Mol Cell Endocrinol* 2010; **322**: 8–28.
64 Detours V, Wattel S, Venet D *et al.* Absence of a specific radiation signature in post-Chernobyl thyroid cancers. *Br J Cancer* 2005; **92**: 1545–52.
65 Port M, Boltze C, Wang Y *et al.* A radiation-induced gene signature distinguishes post-Chernobyl from sporadic papillary thyroid cancers. *Radiat Res* 2007; **168**: 639–49.
66 Detours V, Delys L, Libert F *et al.* Genome-wide gene expression profiling suggests distinct radiation susceptibilities in sporadic and post-Chernobyl papillary thyroid cancers. *Br J Cancer* 2007; **97**: 818–25.
67 Dom G, Tarabichi M, Unger K *et al.* A gene expression signature distinguishes normal tissues of sporadic and radiation-induced papillary thyroid carcinomas. *Br J Cancer* 2012; **107**: 994–1000.
68 Maenhaut C, Detours V, Dom G *et al.* Gene expression profiles for radiation-induced thyroid cancer. *Clin Oncol (R Coll Radiol)* 2011; **23**: 282–8.
69 Mori H, Coleman SM, Xiao Z *et al.* Chromosome translocations and convert leukemic clones are generated during normal fetal development. *Proc Natl Acad Sci USA* 2002; **99**: 8242–7.
70 Lausten-Thomsen U, Madsen HO, Vestergaard TR *et al.* Prevalence of t(12;21) [*ETV6-RUNX1*]-positive cells in healthy neonates. *Blood* 2011; **117**: 186–9.
71 Takahashi M, Saenko VA, Rogounovitch TI *et al.* The *FOXE1* locus is a major genetic determinant for radiation-related thyroid carcinoma in Chernobyl. *Hum Mol Genet* 2010; **19**: 2516–23.
72 Muzza M, Degl'Innocenti D, Colombo C *et al.* The tight relationship between papillary thyroid cancer, autoimmunity and inflammation: clinical and molecular studies. *Clin Endocrinol* 2010; **72**: 702–8.

73 Okayasu I, Saegusa M, Fujiwara M *et al.* Enhanced cellular proliferative activity and cell death in chronic thyroiditis and thyroid papillary carcinoma. *J Cancer Res Clin Oncol* 1995; **121**: 746–52.
74 Guarino V, Castellone MD, Avilla E *et al.* Thyroid cancer and inflammation. *Mol Cell Endocrinol* 2010; **321**: 94–102.
75 Pacini F, Vorontsova T, Molinaro E *et al.* Prevalence of thyroid autoantibodies in children and adolescents from Belarus exposed to the Chernobyl radioactive fallout. *Lancet* 1998; **352**: 763–6.
76 Agata L, Mariotti S, Elisei R *et al.* Thyroid autoantibodies and thyroid function in subjects exposed to Chernobyl fallout during childhood: Evidence for a transient radiation-induced elevation of serum thyroid antibodies without an increase in thyroid autoimmune disease. *J Clin Endocrinol Metab* 2008; **93**: 2729–36.
77 Ostroumova E, Brenner A, Oliynyk V *et al.* Subclinical hypothyroidism after radioiodine exposure: Ukrainian-American cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident (1998–2000). *Environ Health Perspect* 2009; **117**: 745–50.
78 Podtchenko A, Namba H, Saenko VA *et al.* Radiation-induced senescence-like terminal growth arrest in thyroid cells. *Thyroid* 2005; **15**: 306–13.
79 Suzuki K, Yamashita S. Radiation-induced bystander response: Mechanism and clinical implications. *Adv Wound Care* 2014; **3**: 16–24.