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Thyroid disease is a frequent consequence of ionizing radiation

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Long term follow-up of individuals exposed to ionizing radiation during atomic weapons testing, nuclear accidents, and external beam radiation therapy identify thyroid disease, including thyroid cancer, as a major long term consequence. The risk of thyroid carcinoma is directly related to the absorbed dose of radiation, and inversely related to the age of the exposed individual. This manuscript reviews the evidence to support these findings as well as the clinical features of childhood thyroid cancer. The recent molecular changes identified in radiation induced thyroid cancers are compared to the molecular changes found in spontaneous thyroid cancers of children and young adults.

Ionizing radiation damages DNA by inducing thymidine dimerization and DNA base-pair mismatch [1., 2.]. These events are stochastic and have no threshold. However, the probability of DNA damage is increased with an increased number of ionization events (dose). Infrequent DNA base-pair mismatch can be repaired by the DNA mismatch repair enzymes, the most common of which are hMSH-2 and h-MLH-1 [3., 4.]. However, the limited repair capacity can be exceeded, resulting in cell-cycle arrest at the cell-cycle check point. If base-pair mismatch is extensive, the cell is directed into "programmed cell death" or apoptosis. If base-pair mismatch is less extensive, but occurs in critical coding or regulatory elements of an oncogene or tumor suppressor gene, malignant transformation may arise. Thus, radiation-induced activation of oncogenes or inhibition of tumor-suppressor genes may result in somatic tumors. If mutations take place in germ cells, an inherited tumor syndrome could develop.

Well documented follow-up of indi-

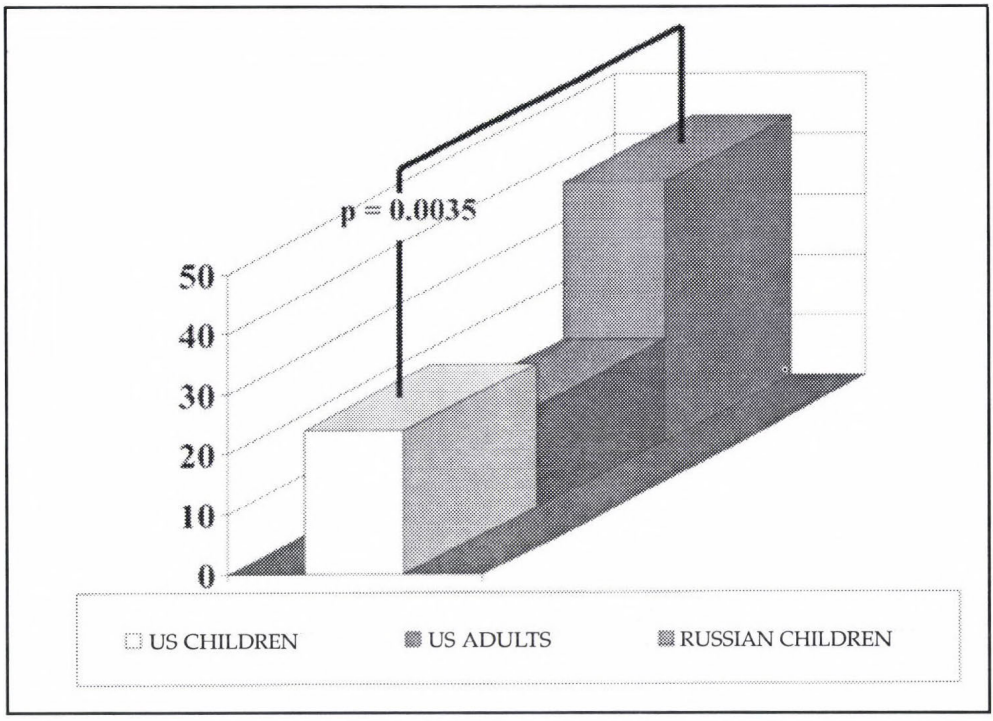

Figure 1.: *VEGF Expression in PTC From US and Russian Subjects. VEGF Expression was determined by immunohistochemistry and Bemi-quantitatively measured as absent/slight, moderate, or intense/diffuse. The percentege of PTC with intense/diffuse staining is presented for spontaneous PTC from US children, spontaneous PTC from US adults, and radiation-induced PTC from children who were < 3 years of ege and living in Bryansk, Russia at the time of the accident.*

viduals with different types of ionizing radiation exposure identify thyroid disease, including thyroid carcinoma, as a major long-term consequence. These include individuals exposed during the Marshall Islands Nuclear Testing Program, children exposed to radioactive debris, food, and milk from the Chernobyl nuclear reactor accident, and individuals treated with external beam radiation therapy for primary malignant or benign diseases. In the following section, the data regarding thyroid disease in these populations is reviewed.

First, we will examine the populátion exposed to radioactive fali-out from the 15 megaton Bravo Nuclear Test which took place in the Marshall Islands on March 1, 1954.5-8 An unexpected change in wind direction spread radioactive fali-out onto the inhabited islands of Rongelap and Utirik. Inhabitants reported seeing the "sun rise in the west" and "snow" which stuck to the skin.s-[9-12]. Due to high ambient radiation levels, the inhabitants were evacuated on the 3rd and 4st of March. However, 28% developed cutaneous radiation burns and 66% developed nausea and vomiting, indicating significant exposure

for the majority of the population [5, 11, 12]. During the ensuing decades, overall survival has been normal, but there have been an increased number of stillborns and miscarriages. This increase was not, however, statistically significant. Ophthalmological and slitlump examinations have been normal, as have growth and development for all children except those who became hypothyroid. Malignant diseases included one case of acute myelogenous leukemia and one skin cancer. Although genetic mutations did not appear to be increased, there was an increased number of dicentric and ring chromosomes, as well as translocations in the cultured lymphocytes from exposed inhabitants. In contrast to the rarity of these events, fully 1/3 developed thyroid disease beginning as early as 9 years after the Bravo test. Benign thyroid adenomas reached a peak incidence in 12 - 14 years, about the time the first thyroid carcinoma appeared (15 years after the test). The peak incidence for thyroid carcinoma occurred somewhat later, between 1980 and 1985 [5, 6, 13].

From this and other studies, it has been well documented that the risk of developing thyroid carcinoma is increased by radiation exposure [4, 15, 16, 17]. Several important relationships between the absorbed dose and characteristics of the irradiated individual have been elucidated. First, the risk of thyroid carcinoma is dose-related with the relatíve risk = 7.7 / Gy absorbed radiation dose.' 8 second, the risk of thyroid carcinoma is age (10 fold higher sensitivity for children) and gender related (2 -4 fold higher sensitivity for girls than boys)'9. Of interest, the histologic type of thyroid carcinoma is related to the iodine content of the diet, so that papillary thyroid carcinoma (PTC) is more likely to develop with high iodine intake, whereas follicular thyroid carcinoma (FTC) is more likely to develop with low iodine intake [19].

A "veritable epidemic" of childhood thyroid carcinoma was reported by DeGroot et al. in 1973 and was almost entirely due to irradiation of children for treatment of benign diseases such as tinea capitis; acne, and thymic enlargement."Fortunately, elimination of radiation therapy for benign disease rapidly followed, and the number of new cases of childhood thyroid cancer quickly declined. However, childhood thyroid carcinoma has become a major world-wide concern following the Chernobyl nuclear accident in 1986. Throughout Belarus and Ukraine; there was little public awareness of the exposure, and no public health programs for removal of contaminated foods or administration of stable iodine prophylaxis. In heavily contaminated regions such as Gomel, the incidence of this previously uncommon disease (1 - 2 / million children) increased by 193-fold [20, 49]. Of great concern, is an increase in the incidence of childhood thyroid carcinoma for countries which were not known to be contaminated, including England and parts of the United States [43, 50].

This should be sharply contrasted with the experience in neighboring

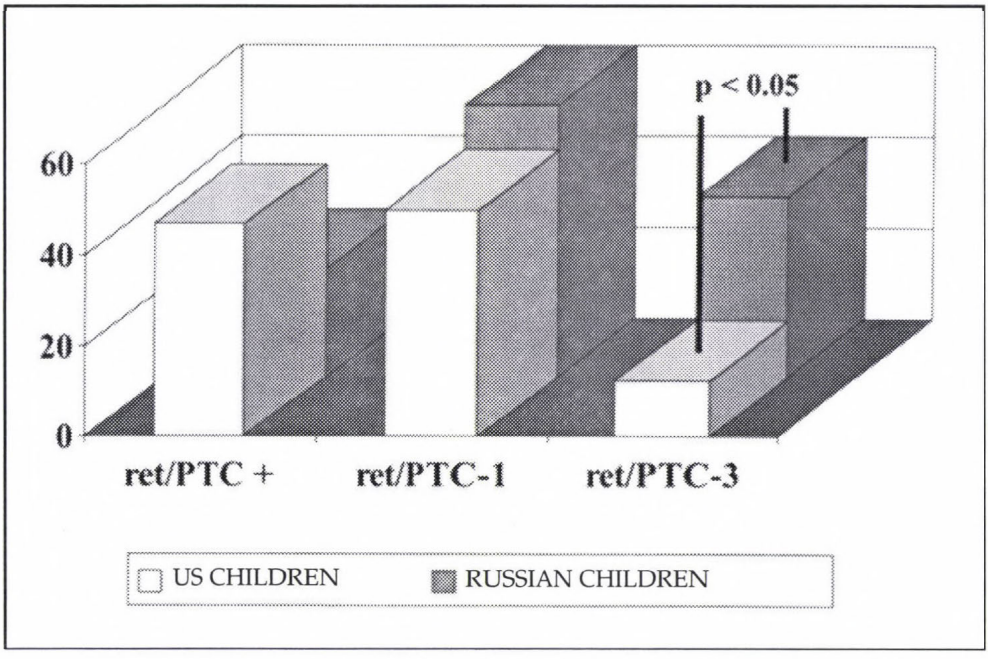

Figure 2.: *Ret/PTC Mutations in PTC from US and Russian Subjects. Tumor RNA was extracted and amplified with intron-spanning primer pairs specific for ret/PTC-1, retJPTC-2 and ret/PTC-3. Data ere compared for spontaneous PTC from US children and radiation-induced PTC from children who were < 3 years of age and living in Bryansk, Russia at the time of the accident. The percentage of PTC with any ret/PTC mutation, ret/PTC-1 mutations, and ret/PTC-3 mutations is shown.*

Poland, where air and water radiation levels were continuously monitored [51, 52]. Increased air and water radiation levels were detected on the second day following the accident, and peaked on the 30th of April. Although rapidly cleared from the atmosphere, radiation levels were still elevated in milk well into May. The Polish government recommended administration of stable iodine prophylaxis (15 mg to newborns, 50 mg to children, and 70 mg to adults) as well as removal of contaminated food and milk products. Ingestion of leafy vegetables was limited for children and pregnant women. By the next day, 10.5 million children and 7 million adults had receíved iodine prophylaxis and perhaps as many as 6% of the population self administered tincture of iodine. Nauman and Wolf reported the long-term follow-up of this experience and found that 95.3% of children receíved at least one dose of stable iodine 53. The only complication was transient hypothyroidism which developed in 0.37% of infants. Of major significance, there has been no increase in the incidence of thyroid nodules, goiter, or thyroid carcinoma. Based on this success, the World Health Organization recommends administration of stable iodine prophy-

laxis for exposed populations stratified according to age. Infants (<3 years of age) should receíve 25 mg, children (3 - 12 years of age) should receíve 50 mg, and older children or adults should receíve 100 mg [51, 54].

The third population of children at increased risk for thyroid carcinoma are survivors of childhood malignancy who were treated with external beam radiation therapy. Survivors of childhood Hodgkin's disease have an 18% risk of second malignancy by 30 years, and a 30-fold increase in the incidence of thyroid carcinoma. However, if they receíved radiation therapy prior to age 4 years, the incidence of thyroid carcinoma is increased by up to 790-fo1d.55 High resolution ultrasound examination has identified abnormal thyroid glands in 100% of patients, and roughly 6.4% have gone on to develop thyroid carcinoma. Similar studies of children treated with external beam radiation therapy for central nervous system prophylaxis against acute lymphoblastic leukemia also report abnormal thyroid ultrasound in 50% of children and a 300-fold increase in the incidence of thyroid cancer [5ó].

These studies clearly identify the thyroid, and especially the thyroid of children, as highly vulnerable to malignant transformation from radiation exposure. Although activation of oncogenes or inactivation of tumor suppressor genes are postulated results from radiation exposure, few studies have examined the pattern of gene expression in radiation induced thyroid cancers compared to spontaneous thyroid cancer [56].

Our laboratory has a major interest in childhood thyroid cancer [57, 69]. For all patients under 21 years of age, thyroid carcinoma is predominantly found in Caucasian females and there is a significant increase in the incidence during puberty [59]. Disease-specific mortality is generally low (under 1 %} but the risk of recurrence is high (19%). Recurrence is more likely to develop in children with large tumors (> 2 cm), multifocal tumors, or more extensive disease at diagnosis (regional lymph node or distant metastasis) [59, 61].

Several tyrosine kinases have been implicated during carcinogenesis, but the vascular endothelial growth factor, VEGF, is frequently implicated in sustaining the growth and even metastasis of many different tumors. We recently examined a cohort of spontaneous and radiation induced childhood thyroid carcinomas for VEGF expression 66.69. We found that expression of both VEGF and the VEGF receptor were increased in PTC compared to normal thyroid, and even greater in radiation-induced PTC *(Figure 1.)*. Most importantly, the only tumors which recurred had intense VEGF expression. Tumors with little of no VEGF expression never recurred. These findings suggest that VEGF is critically important in the clinical behavior of PTC and possibly important in defining the more aggressive clinical course for radiation-induced thyroid carcinoma.

We have also examined these same tumors for the presence of rearrangements in the ret protooncogene which result in the PTC specific gene rearrangements known as ret/PTC-1, ret/PTC-2 and ret/PTC-3 [67, 68]. These mutations splice different upstream regulatory elements onto the tyrosine kinase domain of the ret oncogene and result in unregulated tyrosine kinase activity. We found that ret/PTC rearrangements are more common in childhood (47%) than adulst PTC (3 - 30%). In addition, the rearrangements were predominantly ret/PTC-1 in spontaneous but ret/PTC-3 in radiation-induced childhood PTC *(Figure 2.)*. These observations suggest that the ret/PTC-3 rearrangement may be a particularly frequent result from radiation injury.

In conclusion, thyroid carcinoma is a major risk following radiation exposure from nuclear weapons, reactor accidents, and external beam radiation therapy. Children are at increased risk, and, from all studies, the youngest children have the highest risk of thyroid carcinoma. Prophylaxis, including removal of contaminated food and water as well as stable iodine administration, can be achieved and proved highly effective in Poland. The identity of the oncogenes and tumor suppressor genes that might be damaged from radiation injury is only now being investigated. Recent studies have identified increased expression of VEGF and genetic rearrangements in the ret protooncogene as being of major importance.

REFERENCES

[1] *Aquilina, G., Crescenzi, M., Bignami, M.:* Mismatch repair, G(2)/M cell cycle arrest and lethality after DNA damage. Carcinogenesis 1999; *20:* 2317-26.

[2] *Zeng, M., Narayanan, L., Xu XS, Prolla, T.A., Liskay, R. M., Glazer, P. M.:* Ionizing radiation-induced apoptosis via separate Pms2- and p53- dependent pathways. Cancer Res 2000; *60:* 4889-93.

[3] *Kim, N., Bozek, G., Lo, J. C., Storb, U.:* Different mismatch repair deficiencies all have the same effects on somatic hypermutation: intact primary mechanism accompanied by secondary modifications. J Exp Med 1999; *190:* 21-30.

[4] *Panariello, L., Scarano, M. I., de Rosa, M., et al.:* hMLHI mutations in hereditary nonpolyposis colorectal cancer kindreds. Mutations in brief no. 182. Online. Hum Mutat 1998; *12:* 216-7.

[5] *Howard, J. E., Vaswani, A., Heotis, P.:* Thyroid disease among the Rongelap and Utirik population--an update. Health Phys 1997; *73:* 190-8.

[6] *Dobyns, B. M., Hyrmer, B. A.:* The surgical management of benign and malignant thyroid neoplasms in Marshall Islanders exposed to hydrogen bomb fallout. World J Surg 1992; *16:* 126-39; discussion 139-40.

[7] *Takahashi, T., Simon, S. L., Trott, K. R., et al.:* A progress report of the Marshall Islands nationwide thyroid study: an international cooperative scientific study. Tohoku J Exp Med 1999; *187:* 363-75.

[8] *Yamashita, S., Namba, H., Nagataki, S.:* [Thyroid and radiation]. Nippon Naibunpi Gakkai Zasshi 1993; *69:* 1035-43.

[9] *Simon, S. L., Graham, J. C.:* Dose assessment activities in the Republic of the Marshall Islands. Health Phys 1996; *71:* 438-56.

[10] *Robison, W.L., Noshkin, V.E., Conrado, C. L., et al.:* The Northern Marshall Islands Radiological Survey: data and dose assessments. Health Phys 1997; *73:* 37-48.

[11] *Lessard, E. T., Miltenberger, R. P., Cohn, S. H., Musolino, S. V., Conard, R. A.:* Protracted exposure to fallout: the Rongelap and Utirik experience. Health Phys 1984; *46:* 511-27.

[12] *Larsen, P. R.; Conard, R. A., Knudsen, K. D., et al.:* Thyroid hypofunction after exposure to fallout from a hydrogen bomb explosion. JAMA 1982; *247:* 1571-5.

[13] *Conard, R. A., Meyer, L. M., Sutow, W. W., et al.:* Medical survey of the people of Rongelap and Utirik Islands eleven and twelve years after exposure to fallout radiation (March 1965 and March 1966). Tech Rep Brookhaven Natl Lab *1964:* 1-163.

[14] *Winship ,T., and Rosvall, R. V.:* Childhood thyroid carcinoma. Cancer 1961;14:734-743.

[15] *Duffy, B. J., and Fitzgerald, P. J.:* Cancer of the thyroid in children: A report of 28 cases. J Clin Endocrinol Metab 1950; *10:* 1296-1308.

[16] *Thompson, D. E., Mabuchi, K., Ron, E., et al.:* Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958- 1987 [published erratum appears in Radiat Res 1994 Ju1;139(1):129]. Radiat Res 1994; *137:* 517-67.

[17] *DeGroot, L., Paloyan, E.:* Thyroid carcinoma and radiation. A Chicago endemic. JAMA 1973; *225:* 487-91.

[18] *Ron, E., Lubin, J. H., Shore, R. E, et al.:* Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995; *141:* 259-77.

[19] *Shore, R. E.:* Issues and epidemiological evidence regarding radiation-induced thyroid cancer. Radiat Res 1992; *131:* 98-111.

[20] *Rybakov, S. J., Komissarenko, I. V., Tronko, N. D., et al.:* Thyroid Cancer in Children of Ukraine after the Chernobyl Accident. World J Surg 2000; *24:* 1446-1449.

[21] *Leenhouts, H.P., Brugmans, M. J., Chadwick, K.H.:* Analysis of thyroid cancer data from the Ukraine after 'Chernobyl' using a two-mutation carcinogenesis model [In Process Citation]. Radiat Environ Biophys 2000; *39:* 89-98.

[22] *Jacob, P., Kenigsberg, Y., Goulko, G., et al.:* Thyroid cancer risk in Belarus after the Chernobyl accident: comparison with external exposures. Radiat Environ Biophys 2000; *39:* 25-31.

[23] *Tuttle, R. M., Becker, D. V.:* The Chernobyl accident and its consequences: update at the millennium. Semin Nucl Med 2000; *30:* 133-40.

[24] *Farahati, J., Demidchik, E. P., Biko, J., Reiners, C.:* Inverse association between age at the time of radiation exposure and extent of disease in cases of radiation-induced childhood thyroid carcinoma in Belarus. Cancer 2000; *88:* 1470-6.

[25] *Zanzonico, P. B.:* Age-dependent thyroid absorbed doses for radiobiologically significant radioisotopes of iodine [see comments]. Health Phys 2000; *78:* 60-7.

[26] *Jacob, P., Kenigsberg, Y., Zvonova, I, et al.:* Childhood exposure due to the Chernobyl accident and thyroid cancer risk in contaminated areas of Belarus and Russia. Br J Cancer 1999; *80:* 1461-9.

[27] *Heidenreich, W. F., Kenigsberg, J., Jacob, P., et al.:* Time trends of thyroid cancer incidence in Belarus after the Chernobyl accident. Radiat Res 1999; *151:* 617-25.

[28] *Aurengo, A., Delbot, T., Leenhardt, L., et al.* [Management of 29 children with thyroid cancer following the Chernobyl accident]. Bull Acad Natl Med 1998; *182:* 955-76.

[29] *Astakhova, L.N., Anspaugh, L. R., Beebe, G. W, et al.:* Chernobyl-related thyroid cancer in children of Belarus: a case-control study. Radiat Res 1998; *150:* 349-56.

[30] *Shirahige, Y., Ito, M., Ashizawa, K., et al.:* Childhood thyroid cancer: comparison of Japan and Belarus. Endocr J 1998; *45:* 203-9.

[31] *Karaoglou, A., Chadwick, K. H.:* Health consequences of Chernobyl and other radiation accidents. Report on the European Union Cluster Contractors' workshop (San Miniato, Italy, 17-22 June 1997).

Radiat Environ Biophys 1998; *37:* 1-9.

[32] *Goulko, G. M., Chepurny, N. I., Jacob, P., et al.:* Thyroid dose and thyroid cancer incidence after the Chernobyl accident: assessments for the Zhytomyr region (Ukraine). Radiat Environ Biophys 1998; *36:* 261-73.

[33] *Nagataki, S., Ashizawa, K., Yamashita, S.:* Cause of childhood thyroid cancer after the Chernobyl accident [editorial]. Thyroid 1998; *8:* 115-7.

[34] *Feinmesser, R., Lubin, E., Segal, K., Noyek, A.:* Carcinoma of the thyroid in children--a review. J Pediatr Endocrinol Metab 1997; *10:* 561-8.

[35] *Lomat, L., Galburt, G., Quastel, M. R., Polyakov, S., Okeanov, A., Rozin, S.:* Incidence of childhood disease in Belarus associated with the Chernobyl accident. Environ Health Perspect 1997; 105 Suppl *6:* 1529-32.

[36] *Gembicki. M., Stozharov, A. N., Arinchin, A. N., 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; 105 Suppl *6:* 1487-90.

[37] *Bleuer, J. P., Averkin, Y.I., Abelin, T.:* Chernobyl-related thyroid cancer: what evidence for role of short-líved iodines? Environ Health Perspect 1997; 105 Suppl *6:* 1483-6.

[38] *Harel, G.:* Thyroid cancer following the Chernobyl disaster]. Haxefuah 1997; *133:* 222-4.

[39] *Sobolev, B., Heidenreich, W. F., Kairo, I., Jacob, P., Goulko, G., Likhtarev, I.:* Thyroid cancer incidence in the Ukraine after the Chernobyl accident: comparison with spontaneous incidences. Radiat Environ Biophys 1997; *36:* 195-9.

[40] *van Hoff, J., Averkin, Y. I., Hilchenko, E. I., Prudyvus, I. S.:* Epidemiology of childhood cancer in Belarus: review of data 1978-1994, and discussion of the new Belarusian Childhood Cancer Registry. Stem Cells 1997; *15:* 231-41.

[41] *Krissenko, N.:* Overview of 1993 research activities in Belarus related to the Chernobyl accident. Stem Cells 1997; *15:* 207-10.

[42] Pacim, F., Vorontsova, T., Demidchik, E. *P., et al.:* Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. J Clin Endocrinol Metab 1997; *82:* 3563-9.

[43] *Zimmerman, D. :*Thyroid neoplasia in children [see comments]. Curr Opin Pediatr 1997; *9:* 413-8.

[44] *Robbins, J.:* Lessons from Chernobyl: the event, the aftermath fallout: radioactive, political, social. Thyroid 1997; *7:* 189-92.

[45] *Schwenn, M. R., Brill, A. B.:* Childhood cancer 10 years after the Chernobyl accident. Curr Opin Pediatr 1997; *9:* 51-4

[46] *Antonelli, A., Miccoli, P., Derzhitski, V. E., Panasiuk, G., Solovieva, N., Baschieri, L.:* Epidemiologic and clinical evaluation of thyroid cancer in children from the Gomel region (Belarus). World J Surg 1996; *20:* 867-71.

[47] *Buglova, E. E., Kenigsberg, J. E., Sergeeva, N. V.:* Cancer risk estünation in Belarussian children due to thyroid irradiation as a consequence of the Chernobyl nuclear accident. Health Phys 1996; *71:* 45-9.

[48] *Becker, D. V., Robbins, J., Beebe, G. W., Bouville, A. C., Wachholz, B. W.:* Childhood thyroid cancer following the Chernobyl accident: a status report [published erratum appears in Endocrinol Metab Clin North Am 1996 Jun;25(2):xi]. Endocrinol Metab Clin North Am 1996; *25:* 197-211.

[49] *Ito, M., Yamashita, S., Ashizawa, K., et al.:* Childhood thyroid diseases around Chernobyl evaluated by ultrasound examination and fene needle aspiration cytology. Thyroid 1995; *5:* 365-8

[50] *Mangano, J. J.:* A post-Chernobyl rise in thyroid cancer in Connecticut, USA. Eur J Cancer Prev 1996; *5:* 75-81.

[51] *Becker, D. V., Zanzonico, P.:* Potassium iodide for thyroid blockade in a reactor accident: administrative policies that gov-

ern its use. Thyroid 1997; *7:* 193-7.

[52] *Gembicki, M., Sowinski, J,. Ruchala, M., Bednarek, J.:* Influence of radioactive contamination and iodine prophylaxis after the Czernobyl disaster on thyroid morphology and function of the Poznan region]. Endokrynol Pol 1991; *42:* 273-98.

[53] *Nauman, J., Wolff, J.:* Iodide prophylaxis in Poland after the Chernobyl reactor accident: benefits and risks. Am J Med 1993; *94:* 524-32.

[54] Nuclear accident. World Health Organization. Int Nurs Rev 1986; *33:* 123-4.

[55] *Shafford, E. A., Kingston, J. E., Healy, J. C., Webb, J. A., Plowman, P. N., Reznek, R. H.:* Thyroid nodular disease after radiotherapy to the neck for childhood Hodgkin's disease. Br J Cancer 1999; *80:* 808-14.

[56] *Mohn, A., Chiarelli, F., Di Marzio, A., Impicciatore, P., Marsico ,S., Angrilli, F.:* Thyroid function in children treated for acute lymphoblastic leukemia. J Endocrinol Invest 1997; *20:* 215-9.

[57] *Degnan, B. M., McClellan, D. R., Francis, G. L.:* An analysis of fine-needle aspiration biopsy of the thyroid in children and adolescents. J Pediatr Surg 1996; *31:* 903-7.

[58] *McClellan, D. R., Francis, G. L.:*Thyroid cancer in children, pregnant women, and patients with Graves' disease. Endocrinol Metab Clin North Am 1996; *25:* 27-48.

[59] *Welch, Dinauer, C. A., Tuttle, R. M., Robie, D. K., et al.:* Clinical features associated with metastasis and recurrence of differentiated thyroid cancer in children, adolescents and young adults. Clin Endocrinol (Oxfj 1998; *49:* 619-28. ,

[60] *Robie, D. K., Dinauer, C. W., Tuttle, R. M., et al.:* The impact of initial surgical management on outcome in young patients with differentiated thyroid cancer. J Pediatr Surg 1998; *33:* 1134-8; discussion 1139-40.

[61] *Welch, Dinauer, C. A., Tuttle, R. M., Robie, D. K., McClellan, D. R., Francis, G. L.:* Extensive surgery improves recurrence-free saruival for children and young patients with class I papillary thyroid carcinoma. J Pediatr Surg 1999; *34:* 1799-804.

[62] *Fenton, C., Anderson, J., Lukes, Y., Dinauer, C. A., Tuttle, R. M., Francis, G. L.:* Ras mutations are uncommon in sporadic thyroid cancer in children and young adults. J Endocrinol Invest 1999; *22:* 781-9.

[63] *Ringel, M. D., Balducci-Silano, P. L., Anderson, J. S., et al.:* Quantitative reverse transcription-polymerase chain reaction of circulating thyroglobulin messenger ribonucleic acid for monitoring patients with thyroid carcinoma. J Clin Endocrinol Metab 1999; *84:* 4037-42.

[64] *Wingo, S. T., Ringel, M. D., Anderson, J. S., et al.:* Quantitative reverse transcription-PCR measurement of thyroglobulin mRNA in peripheral blood of healthy subjects. Clin Chem 1999; *45:* 785-9.

[65] *Fenton, C. L., Patel, A., Tuttle, R. M., Francis, G. L.:* Autoantibodies to p53 in sera of patients with autoimmune thyroid disease. Ann Clin Lab Sci 2000; *30:* 179-83.

[66] *Fenton, C., Patel, A., Dinauer, C., Robie, D. K., Tuttle, R. M., Francis, G. L.:* The expression of vascular endothelial growth factor and the type 1 vascular endothelial growth factor receptor correlate with the size of papillary thyroid carcinoma in children and young adults. Thyroid 2000; *10:* 349-57.

[67] *Fenton, C. L., Lukes, Y., Nicholson, D., Dinauer, C. A., Francis, G. L., Tuttle, R. M:.* The ret/PTC mutations are common in sporadic papillary thyroid carcinoma of children and young adults. J Clin Endocrinol Metab 2000; *85:* 1170-5.

[68] *Tuttle, R. M. F. C., Lukes, Y., Davis, S., Kopecky, K. J., Reinhardt, B., Lushnikov, E., Abrosimov, A., Troshin, V., Tsyb, A., and Francis, G.:* Activation of the ret/PTC oncogene in papillary thyroid cancer from Russian children exposed to radiafion following the Chernobyl accident. 12`" International Thyroid Conference, Kyoto, Japan. Presented October, 2000.

[69] *Tuttle, R. M. P. A., Francis, G., Davis, S., Kopecky, K. J., Lushnikov, E., Abrosimov, A., Troshin, V., Tsyb, A., and Fenton, C.:* Vascular endothelial growth factor

(VEGF) and Type 1 VEGF receptor ~Flt-1) are highly expressed in Russian papillary thyroid carcinomas. 12tn International Thyroid Conference, Kyoto, Japan. Presented October, 2000.

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Az ionizáló sugárzások hatása a pajzsmirigy megbetegedésének kialakulására

Az atomfegyver, a nukleáris balesetek és a gyógyászati alkalmazás késői következményeit vizsgálva megállapították, hogy a késői következmények rákos megbetegedések formájában jelentkeznek. Ezek előfordulásának száma függ az abszorbeált dózistól és fordítottan arányos az életkorral. A beszámoló a gyermekkori rákos megbetegedések kérdéseivel foglalkozik megállapítva, hogy milyen molekuláris változások jelentkeznek az ionizáló sugárzás okozta és a spontán fellépő pajzsmirigy tumorok esetében gyermekkorban és az ún. „fiatal" felnőtteknél.

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