Radiation-induced Thyroid Cancer—What’s New?

John D. Boice, Jr.

Several years ago I wrote that there was little more to be learned about radiation-induced thyroid cancer (1). I was mistaken. After 50 years of research, it was known that the thyroid gland of children, but not adults, was especially sensitive to the carcinogenic action of ionizing radiation, that a straight line adequately represented the relationship between dose of radiation and effect, that effects for thyroid cancer were seen at lower dose levels (on the order of 0.10 Gy) than those observed for most other radiation-induced cancers, that very high dose levels resulted in a lowering of risk because of cell killing, that screening had a profound influence, and that mixtures of radioiodines could cause thyroid cancer. However, the carcinogenic effect of $^{131}$I exposure of children was uncertain. The article by Cardis et al. (2) in this issue of the Journal has provided new and, if confirmed, provocative information on the risk of radiation-induced thyroid cancer and on the modifying role of diets deficient in stable iodine and of administering iodine supplements months after the exposure has occurred.

Cardis et al. (2) conducted a case–control study of thyroid cancer among children who were younger than the age of 15 years in 1986 and who lived in areas of radioactive fallout from the Chernobyl nuclear reactor accident. There were 276 children with confirmed diagnoses of thyroid cancer and 1300 matched control subjects for whom questionnaire data were obtained on diet; response rates differed somewhat between case patients (>$98%) and control subjects (58%–85%). Children were residing in one of two administrative regions in Belarus or one of four administrative regions in the Russian Federation. Although thyroid cancer surgeries occurred between 1992 and 1998 (i.e., 6–13 years after the reactor accident), the methods of ascertainment and years of coverage differed between regions, in part to avoid overlap with previously reported investigations (3,4). A comprehensive dose reconstruction program estimated radiation dose to the thyroid from the inhalation or ingestion of $^{131}$I, other short-lived radioactive iodine isotopes ($^{132}$I, $^{133}$I, and $^{135}$I), radioactive tellurium isotopes ($^{131}$Te and $^{132}$Te), and radioactive cesium isotopes ($^{134}$Cs and $^{137}$Cs), and external $\gamma$-ray exposures from radioactive elements deposited on the ground. The major contribution to dose was from drinking milk contaminated with $^{131}$I, which because of its 8-day half-life takes several months to deposit its energy in the thyroid gland after ingestion. The median thyroid dose was about 0.35 Gy, and the maximum dose was 10.2 Gy. Most of the areas studied were rural. Diets were deficient in stable iodine, which apparently was a feature in practically all of these heavily exposed regions in 1986 (5,6). Iodine deficiency was evaluated as a cofactor, modifying the effect of radiation. Dietary supplements containing potassium iodide were also evaluated.

Similar to previous case–control (3,4) and ecologic (7) studies of persons exposed as children to radioactive iodines from the Chernobyl accident, a substantial increase in thyroid cancer was reported that was related to the estimated radiation dose to the thyroid gland. Statistically significant excesses of thyroid cancers were reported relatively early after exposure compared with studies of external $x$-ray or $\gamma$-ray exposure (6,8), apparently attributable to the very large numbers of children exposed in Belarus and the Russian Federation. It seems possible, however, that increased surveillance and early detection may have contributed to the early excess (6,9), and the impact of screening and case detection on thyroid cancer risk estimation has yet to be fully explored. The most sensitive group was studied (i.e., children younger than 15 years at exposure), and it would have been informative to learn whether exposure of children younger than 2 years was associated with a higher risk than exposure of children at older ages, as has been reported in studies of external radiation (6,8). A linear dose–response relationship was highlighted, but this relationship was evident over a selected range of the data and not for the full range for which a linear-quadratic dose–response model provided the best fit. One may argue whether selecting the dose range for analysis after the data are collected is appropriate, especially given the uncertainties in retrospective dose estimation and because the excluded dose range is not known to increase cell killing. Nonetheless, the estimates of risk were substantial regardless of the dose–response model used or dose range evaluated with the odds ratios at 1 Gy of between 4.85 and 8.44. The estimate of radiation-induced thyroid cancer was similar between boys and girls. An impressive effort was made to reconstruct radiation doses. Some uncertainties remain, however, regarding the accuracy of dietary recall some 6–13 years or more after exposure in childhood, the likely influence of screening and surveillance, the possibility of response bias between case patients and control subjects, and the contribution to risk of the short-lived radionuclides other than $^{131}$I; i.e., although the median dose was low for these other radionuclides, the maximum was 0.5 Gy (6,10).

The findings from Cardis et al. (2), however, newly suggest that diets deficient in stable iodine potentiate the risk of radiation-induced thyroid cancer and that continued use of dietary supplements containing potassium iodide substantially reduces the risk of radiation-induced thyroid cancer, even if taken many months or years after the exposure has occurred. The first observation would caution against generalizing the Chernobyl findings to other exposed populations of children whose diets are not deficient in iodine. The second finding might have substantial public health and clinical implications if continued administration

Affiliation of author: International Epidemiology Institute, Rockville, MD and Vanderbilt University School of Medicine, Nashville, TN.

Correspondence to: John D. Boice, Jr., ScD, International Epidemiology Institute, 1455 Research Blvd., Ste. 550, Rockville, MD 20850 (e-mail: john.boice@vanderbilt.edu).

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of potassium iodide reduces the risk of radiation-induced thyroid cancer and presumably other types of thyroid cancer, at least in areas of endemic goiter or iodine deficiency.

Cardis et al. (2) conclude that the risk of radiation-induced thyroid cancer was similar to, though somewhat lower than, that observed in studies of children exposed to external radiation (18). Interpretation is somewhat problematic, however, because the risk from the exposure to radiiodines appeared concentrated among children residing in severe iodine-deficient areas (i.e., where the radiation risk was three times higher than the risk observed in children residing in the areas of less severe iodine deficiency). Conceivably, the elevated radiation risk reflects an interaction with a dysfunctional thyroid gland; this result tempers conclusions with regard to similarities or dissimilarities in risk observed in other studies of children with normal glands. The thyroid gland of children proliferates more rapidly than the adult gland, and it is believed that this rapid cell growth is the primary reason why radiation effects are so apparent after exposures in childhood and not among adults (11). The thyroid glands of children living in areas of iodine deficiency are also more active and undergo more cellular proliferation and growth than in areas of iodine sufficiency, and it may be that this enhanced cellular activity is related to the enhanced risk observed. Thus, the growing thyroid glands of children coupled with an abnormal growth potential related to iodine deficiency may enhance the expression of cellular damage induced by radiation. It is then noteworthy that children who may have had normal functioning thyroid glands because of residing in the areas of highest iodine soil content and who subsequently took potassium iodide supplements were not at a statistically significantly increased risk of developing thyroid cancer after the radiation exposures (odds ratio at 1 Gy = 1.08, 95% confidence interval = 0.3 to 3.6).

It is somewhat remarkable that potassium iodide administered months after exposure would reduce risk at all because the radio-active iodines would have already been absorbed and because there would be no blockage in uptake that would have reduced thyroid dose. Yet a threefold reduction in risk was observed among children given potassium iodide as a dietary supplement compared with those without such an administration. The authors speculate that the continued administration of this potassium iodide supplement reduced the size of the thyroid gland in these areas of iodine deficiency and that this reduction in cellular proliferation resulted in a reduced thyroid cancer risk. Whether such a protection would occur in areas of iodine sufficiency is unclear and apparently could not be evaluated in the current investigation, because all the areas studied had some level, however mild, of iodine insufficiency in 1986.

The magnitude of the risk of thyroid cancer following 131I exposures has been a matter of debate for more than 30 years (12,13). A lower risk from 131I compared with brief exposures to external radiation might be anticipated because delivery of the 131I dose to the thyroid gland is gradual, occurring over at least a month, and would allow more opportunities to repair DNA damage. Further, the distribution of 131I within the gland and the energy of the emitted β particles are such that a nonuniform exposure to the thyroid gland would likely result and carry a lower risk potential than if the thyroid gland were more uniformly exposed (12,13).

Studies of other populations exposed to fallout from weapons testing in the South Pacific could not evaluate an independent effect for 131I because the contributions of the other radioactive iodines and of external radiation were substantial (14). Studies of radioactive fallout from the Nevada test site indicated a lower contribution of the shorter-lived radioactive iodines, and the risk of thyroid cancer was not statistically significantly increased (15). Three studies that included more than 6000 children administered known amounts of 131I for diagnostic purposes (mean dose = 1 Gy) also fail to report an increased risk of thyroid cancer (nine total cases reported and about nine expected), but the numbers of children exposed under the age of 10 are small (16–18). More recently, a comprehensive study of exposure of 3440 young children in the 1940s–1950s to fallout from essentially pure 131I from the Hanford nuclear site did not find an increased risk of thyroid cancer at doses on the order of 0.17 Gy (maximum dose ≥1 Gy) that was based on 19 observed cancers (19).

There is no question that the Chernobyl fallout has resulted in a substantial increase in thyroid cancer in heavily exposed populations, and Cardis et al. (2) now provide the most comprehensive and quantitative assessment of risk to date. Yet some questions remain. Is there a statistically significant increase in cancer among children with normal functioning thyroid glands that can be attributed to radioiodine exposure? Can the role of screening and case detection be quantified? Is the risk of thyroid cancer among children younger than 2 years at exposure substantially higher per unit dose than the risk of exposure at older ages? What is the pattern of risk by age at observation; i.e., is there a plateau after adolescence or will risk decrease or increase? Although 131I is the major contributor to dose, can the contribution of risk from the shorter-lived radioiodines be quantified? Why should the shape of the dose–response curve change over dose ranges where cellular killing is unlikely? Would potassium iodide supplements administered months after exposure reduce the risk of radiation-induced thyroid cancers in areas that are not deficient in iodine? New studies in the Ukraine (20,21) and elsewhere may provide additional knowledge and further the advances in understanding made by the current investigation (2).

References