Radiation and Thyroid Cancer

What More Can be Learned?

John D. Boice, Jr

From the International Epidemiology Institute, Rockville, Maryland, USA

Correspondence to: Dr John D. Boice, Jr, Scientific Director, International Epidemiology Institute, 1550 Research Blvd, Suite 200, Rockville, Maryland 20850-3127, USA. Tel: +1 301 517 4021. Fax: +1 301-517-4063. E-mail BoiceJ@Compuserve.com

Acta Oncologica Vol. 37, No. 4, pp. 321–324, 1998

Received 16 January 1998
Accepted 4 March 1998

As we enter the next millennium, perhaps it is time to pause and ask what more can be learned about the adverse effects from excessive exposure to ionizing radiation. Ionizing radiation causes cancer in humans, that no one will dispute. This cannot be said convincingly of a world of other common environmental exposures such as, for example, non-ionizing electromagnetic fields. In fact, as Hall & Holm (1) so clearly present, we know more about radiation-induced cancers in general, and radiation-induced thyroid cancers in particular, than virtually any other human carcinogen. There are nearly 20 well-designed epidemiologic studies with individual estimates of radiation dose to the thyroid gland (see Table 1). They include radiotherapy studies of newborn infants with enlarged thymus glands or hemangiomas, children with ringworm of the scalp, adolescents with enlarged tonsils, children with cancer, young adults with Hodgkin's disease, women with cervical cancer, patients given bone marrow transplants. Studies of internally ingested radioactive iodines include patients administered ^{131}I for diagnostic purposes, patients with hyperthyroidism treated with ^{131}I, Marshall Islanders exposed to massive amounts of fallout from a nuclear weapon tests. There are occupational studies of radiologists and, most importantly, studies of thyroid cancer incidence among Japanese atomic bomb survivors. It is perhaps noteworthy that studies conducted in the former Soviet Union have yet to be added to this list of studies that have provided quantitative data on risk. To date, the ecological investigations of thyroid cancer have demonstrated a remarkable increase in risk among children living near Chernobyl but there is a paucity of dosimetric data and the powerful influence of screening has been difficult to evaluate. However, the many high quality studies conducted over many decades in many countries by different investigators have provided insights into the patterns of risk following irradiation (2).

The more than 50 years of study of radiation-induced thyroid disease can be summarized as follows:

- The age makes the poison.
- The response is linear.
- The relative risk is high.
- Low doses (0.1 Sv) pose a hazard.
- Very high doses (40 Sv) pose a low risk.
- Chronic exposure is somewhat less risky than brief exposure.
- Relative risk decreases with time.
- The minimal latent period is 5–9 years.
- Women are more vulnerable.
- Screening has a profound influence.
- Radioiodines pose a risk.
- ^{131}I risk is not clarified in children.

The age makes the poison. Industrial hygienists commonly state that the 'dose makes the poison.' This is generally true in radiation epidemiology with higher doses rendering more risk than lower ones, although for purposes of radiation protection it is assumed that low doses do pose a risk, albeit a very low one. For radiation-induced thyroid cancer, however, age may be more influential than dose. The epidemiologic literature is consistent in revealing that age at exposure exerts a remarkable and powerful influence on risk. So much so that for exposures after reaching the age of 20, the associated radiation risk appears minimal for both external radiation and internal ^{131}I (2, 5). The biological activity of the thyroid gland during childhood might be related in part to the enhanced sensitivity to carcinogenic influences. When studies are reported indicating high risks following exposures in adulthood, it might be advisable to seek a non-radiation explanation.

 ISSN 0284-186X

Table 1

Cohort studies of radiation-induced thyroid cancer

Study	No. Exposed	Observed Cases	Expected Cases	Mean Dose (Sv)	Excess RR Per Sv
Cohort studies in children					
A-Bomb Survivors (0–19 yrs)	17 375	59	22.2	0.26	6.3 (5.1–10.1)
Israeli *Tinea Capitis*	10 834	43	10.7	0.1	34.0 (23–47)
Rochester Thymus	2 652	37	2.7	1.4	9.5 (6.9–12.7)
LESG Childhood Cancer	9 170	23	0.4	12.5	4.5 (3.1–6.4)
Swedish Hemangioma	14 351	17	7.5	0.26	4.9 (1.2–10.1)
Boston Lymphoid Hyperplasia	1 192	13	5.4	0.24	5.9 (1.8–12)
Chicago Tonsil	2 634	309	110.4	0.60	3.0 (2.6–3.5)
Bone Marrow Transplant	14 656*	8	~1.0	~12	0.6 (0.1–1.0)
LESG Hodgkin's Disease	1 380	10	0.31	~40	0.8 (0.4–1.5)
Nordic Hodgkin's Disease	1 641	9	0.27	~40	0.8 (0.4–1.5)
Marshall Islanders (0–18 yrs)	127	6	1.1	11.5	0.4 (0.1–1.0)
Cohort studies in adults					
A-Bomb Survivors (20+yrs)	20 458	73	67.1	0.26	0.3 (<0–12), ns
Cervical Cancer	82 616	16	12.5	0.11	2.5 (<0–6.8), ns
Stanford Hodgkin's Disease	1 787	6	0.4	45	0.3 (0.1–0.7)
Swedish Diagnostic ^{131}I	34 104	67	49.7	1.1	0.3 (0.1–0.6)
Swedish Hyperthyroidism (^{131}I)	10 552	18	14.0	100	0.0
Chinese Medical x-ray Workers	27 011	8	4.8	~1	0.7 (<0–3.7), ns

Sources: UNSCEAR (2); Shore (3); Boice et al. (4)
* Includes patients over 20 years of age.
ns, not statistically significant (95% confidence interval).

The response is linear and the risk coefficient is high. A straight line adequately fits the data on radiation-induced thyroid cancer following exposures in childhood (6). Similarly, significant excess risks have been noted at low doses, on the order of 0.1 Sv (100 mSv). Dose delivery in fractions appears to carry a slightly lower risk than acute exposures. Furthermore, the ERR/Sv of 7.7 for childhood exposures (6) is substantially higher than the risk coefficient reported for all other solid tumors, 0.63 (5).

Very high doses (40 Sv) pose a low risk (7) compared to more moderate exposures. Clinically, patients treated for Hodgkin's disease with external radiation and for hyperthyroidism with ^{131}I can receive very high doses to the thyroid gland, as can children treated for various forms of cancer. Comprehensive large-scale studies indicate a lower risk following such ablative doses, related in part to the destruction of cells from such high deposition of energy. Cells that are incapable of dividing are incapable of cancerous growth.

Screening has been demonstrated to bring about greatly increased detection of indolent thyroid cancers, both occult and non-occult. Bias occurs when an exposed group is screened and the comparison group is not. A novel study of children with lymphoid hyperplasia found a high risk of thyroid neoplasm based on questionnaire responses from exposed and non-exposed (surgical) patients. However, upon clinical examination of both groups, the risk coefficient was calculated to be much lower than based on the questionnaire data alone. It was determined that the awareness of prior exposure for enlarged tonsils caused the irradiated patients to seek prior medical attention, whereas the non-exposed surgical patients did not avail themselves of such self-screening (8).

Some of the difficulty in interpreting the remarkable excess of thyroid cancer among children exposed to Chernobyl fallout relates to the screening influence. It is not disputed that the excess occurrence is phenomenal, although the actual number of deaths related to thyroid cancer is very small, perhaps less than 5. While the tumors are aggressive, this is not unusual for childhood thyroid cancer (9). A portion of the risk might also be related to the short-lived radioiodines (other than ^{131}I), as was the case in the Marshall Islands, where dose is delivered more uniformly across the thyroid gland and at a high rate. Screening clearly had some influence but the effect is difficult to quantify. The minimal latency period seems too short, within 4–5 years, and the absence of individual dosimetry is a big limitation. Because much of the dosimetry will have to be based on dietary recall, i.e., how much milk was consumed during a few months over 10 years ago, it will be difficult to quantify the radiation risk, at least one that is based on individual dose reconstruction. Measurements of radioactivity in the thyroid gland made shortly after the accident, however, have the potential to provide more quantitative data on dose. Because dose to individuals has not yet been reported, most of the studies conducted to date are 'ecological'. Such geographical correlation studies are the weakest type of epidemiologic investigation because of the increased susceptibility to bias.

Recall and observational bias may also have played a role in the studies of thyroid cancer in the USA related to nuclear weapons tests. There was no differences in regional rates of thyroid cancer between high and low fallout regions, but a radiation association was suggested on the basis of individual dose estimates from dietary recall. However, the analytic study was not without problems. Methodologic concerns included the non-blinded nature of the interviews and the apparent over-referral for physical examination of persons known to reside in high-fallout regions (2). This study exemplifies how the absence of dose information can lead to misinterpretation when only ecological data are relied upon, although in this case the dosimetric study of individuals might also have been misleading for other reasons.

In an early study, using ultrasound and physical examination, it was found that persons residing in villages exposed to high and low levels of Chernobyl fallout showed no difference in thyroid abnormalities. A more recent survey with longer follow-up, however, has recently been published (10). Two villages in the Bryansk region of Russia were evaluated 7 years after the accident. High prevalences of thyroid abnormalities were found in the contaminated village for children < 10 years old at exposure (8.1%) compared to children living in the uncontaminated village (1.6%). There were no differences in nodularity among those over age 10 years (18.8% vs. 17.7%) in 1986. A mean dose of 516 mSv was possible, with some doses as high as 10–40 Sv. The mixture of radioiodines may have played a role. Genetic susceptibility and the influence of endemic goiter were also mentioned as potential contributors to risk. Unfortunately, exact quantification of risk does not seem possible. Nonetheless, the data are consistent with a high risk of thyroid neoplasm being concentrated only among the young at exposure and suggest that the thyroid doses may have been large and partially due to shorter lived isotopes of iodine.

The importance of age at exposure in interpreting study results is also exemplified in a recent report from the former Soviet Union that purports a high radiation risk coefficient among adult Chernobyl cleanup workers (11). Because significantly high-risk coefficients have never been reported in any large-scale epidemiologic studies of adults, perhaps the principle of parsimony (Occam's Razor) might be applied. Paraphrasing: 'Choose the simplest explanation that requires the fewest assumptions.' Instead of concluding that Chernobyl cleanup workers are at similar risk of radiogenic thyroid cancer (ERR/Sv, 5.3) as exposed children (ERR/Sv, 7.7), that high risks occur within 3 years of exposure and that the large compendium of current knowledge on adult exposures might be in error, perhaps alternative and simpler explanations should be given more weight, such as the pronounced effect of special medical surveillance among emergency workers, the use of national rates for comparisons, and not using individual dosimetry for internal comparisons (12).

Regarding ^{131}I risks, studies of adult populations exposed to high and low doses of ^{131}I for medical purposes indicate no or very low risk. Studies of childhood exposure to ^{131}I are inconclusive, largely because of the small numbers studied. Studies of Chernobyl populations remain difficult to interpret due to the influence of screening and the potential impact of radioiodines other than ^{131}I. ^{131}I, similar to all other forms of radiation, appears not to cause thyroid cancer after exposures in adulthood to any measurable extent. The risk for childhood exposure, however, has yet to be quantified.

Given dwindling resources for radiation studies, where should future efforts be focused? After separating the fact from fiction as Hall & Holm (1) have done, is there much more that can be learned from studies of radiation-induced thyroid cancer? Quantifying the risk of ^{131}I exposures in children, while scientifically interesting, may not be of highest priority or importance. We know that radiation exposure in childhood is risky and it is unlikely that ^{131}I carries a greater risk than what is computed for external radiation (although the risk may be lower). Some of the more fruitful areas of research might include studies of high-dose medical radiation where somatic cell rearrangements might suggest molecular mechanisms for action (e.g., RET oncogene studies). Furthermore, it might be asked why children (and girls) are so remarkably vulnerable to radiation-induced thyroid cancer. Why do age and hormonal influences related to gender have such a powerful influence on radiation risk? Studies of children treated with radiation for cancer might also evaluate the role, if any, that underlying host factors might play in enhancing the carcinogenic action of radiation (13). Since there are many millions of persons in the world exposed each year to x-rays, perhaps more effort should be directed toward studying medical exposures. Studies to learn more about the mechanisms by which radiation causes cancer should be given more support, as should those in medical settings where most of the world's exposures occur.

A recent scientific correspondence calculates the thyroid cancer risk to children following the Chernobyl reactor accident. Extensive dosimetric evaluations in 3 countries were applied to compute the excess RR per Sv of 22–90 based on over 400 cases. These high estimates may reflect the short follow-up compared with other studies (Table 1) as well as the screening bias discussed earlier. Unfortunately, the analysis remains ecological because doses to individuals with thyroid cancer are not presented and only grouped area comparisons are made, complicating the interpretation of the purported dose response (14).

REFERENCES

1. Hall P, Holm L-E. Radiation-associated thyroid cancer—facts and fiction. Acta Oncol 1998; 37: 325–30.

2. United Nations Scientific Committee on the Effects of Atomic Radiation. UNSCEAR 1994 Report to the General Assembly, with Scientific Annexes. Sources and Effects of Ionizing Radiation. E.94.IX11. New York: United Nations, 1994.
3. Shore RE. Human thyroid cancer induction by ionizing radiation: summary of studies based on external irradiation and radioactive iodines. In: Karagoglou A, Desmet G, Kelly GN, Menzel HG, eds. The radiological consequences of the Chernobyl accident. Luxembourg: Office for Official Publications of the European Communities, 1996: 669–75.
4. Boice JD Jr, Land CE, Preston D. Ionizing radiation. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. New York: Oxford University Press, 1996: 319–54.
5. Thompson DE, Mabuchi K, Ron E, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. Radiat Res 1994; 137: S17–67.
6. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995; 141: 259–77.
7. Hancock SL, McDougall IR, Constine LS. Thyroid abnormalities after therapeutic external radiation. Int J Radiat Oncol Biol Phys 1995; 31: 1165–70.
8. Pottern LM, Kaplan MM, Larsen PR, et al. Thyroid nodularity after childhood irradiation for lymphoid hyperplasia: a comparison of questionnaire and clinical findings. J Clin Epidemiol 1990; 42: 449–60.
9. Robbins J. Lessons from Chernobyl: the event, the aftermath fallout: radioactive, political, social. Thyroid 1997; 7: 189–92.
10. Kumpusalo L, Kumpusalo E, Soimakallio S, et al. Thyroid ultrasound findings 7 years after the Chernobyl accident. A comparative epidemiological study in the Bryansk region of Russia. Acta Radiol 1996; 37: 904–9.
11. Ivanov VK, Tsyb AF, Gorsky AL, et al. Thyroid cancer among 'liquidators' of the Chernobyl accident. Br J Radiol 1997; 70: 937–41.
12. Boice JD Jr, Holm L-E. Leukaemia and thyroid cancer in emergency workers of the Chernobyl accident: estimation of radiation risks. [Letter]. Radiat Environ Biophys 1997; 36: 213–4.
13. deVathaire F, Francois P, Schlumberger M, et al. Epidemiological evidence for a common mechanism for neuroblastoma and differentiated thyroid tumour. Br J Cancer 1992; 65: 425–8.
14. Jacob P, Goulko G, Heidenreich WF, et al. Thyroid cancer risk to children calculated. Nature 1998; 392: 31–2.