^{131}I Ablation Treatment in Young Females After the Chernobyl Accident

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The Chernobyl accident resulted in a number of cases of thyroid cancer in females under the age of 20 y. Many of these individuals were treated with surgical removal of the thyroid gland followed by ^{131}I ablation of residual thyroid tissue. Epidemiologic evidence demonstrates that ^{131}I treatment for thyroid cancer or hyperthyroidism in adult women confers negligible risk of breast cancer. However, comparable data for younger women do not exist. Studies of external radiation exposure indicate that, for radiation exposures of as low as 0.2–0.7 Gy, the risk of breast cancer is greater for infant and adolescent female breast tissues than for adult female breast tissues. **Methods:** The effective half-time of ^{131}I measured in athyrotic patients was used together with the OLINDA/EXM computer code to estimate doses to breast tissue in 10-y-old, 15-y-old, and young adult females from ablation treatment. **Results:** The dose to pediatric and young adult female breast tissue associated with a 5.6-GBq (150 mCi) ablation treatment may range from 0.35 to 0.55 Gy, resulting in a lifetime risk of breast cancer ranging from 2–4 cases per 100 such individuals exposed and a lifetime risk of solid tumors ranging from 8 to 17 solid tumors per 100 such individuals exposed. Administration of multiple ablation treatments, as often occurs with metastases, could result in doses ranging from 0.7 to 1 Gy, with corresponding increases in the lifetime cancer risk. **Conclusion:** These estimates suggest the need for additional research and a possible need for surveillance of young Chernobyl thyroid cancer patients who received ^{131}I ablation treatment.

Key Words: thyroid cancer; ^{131}I; breast cancer; ablation treatment; Chernobyl

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Radioactive iodine is routinely used in a variety of diagnostic and therapeutic procedures (primarily related to treatment of hyperthyroidism and thyroid cancer). Epidemiologic studies to date have found no increase in overall cancer mortality associated with treatment using ^{131}I (*1–4*). However, the Chernobyl accident was unique in that a large number of girls (most under the age of 5 y at the time of exposure and about 12 y old at diagnosis) were treated with ^{131}I for thyroid cancer. Treatment for this condition consists of surgical removal of the thyroid followed by high-dose ^{131}I ablation treatment. The dose to residual thyroid tissue received during ablation treatment can be 100–1,000 times larger than the ^{131}I dose to the thyroid received after the Chernobyl accident. There is no increased risk of thyroid cancer from the ablation treatment, because the thyroid has been removed. However, the possibility exists that breast tissue in women younger than 20 y may receive significant radiation doses from these ^{131}I exposures. Arguing against this possibility are multiple epidemiologic studies of adult women treated with ^{131}I that have so far been negative for increased rates of breast cancer (*2–4*). In addition, it is generally believed that normal breast tissue does not take up significant quantities of radioactive iodine. However, because the breast is one of the more radiosensitive tissues in the body, the possibility exists that young females treated with radioactive iodine ablation after the Chernobyl accident may have an observable increase in the incidence of breast cancer later in life. The purpose of this study was to characterize the dose to breast tissue in 10-y-old, 15-y-old, and young adult females from iodine ablation treatment after the Chernobyl accident and to determine whether long-term epidemiologic surveillance of these young patients may be warranted.

The typical ablation treatment for thyroid cancer in adults consists in administering 1.1–5.6 GBq (30–150 mCi) of ^{131}I as sodium iodide. This activity would result in a dose of 400–1,950 Gy to a normal thyroid (assuming a thyroid tissue dose conversion factor of 0.35 Gy/MBq), but because thyroid remnants have less than the normal iodine uptake, and because the retention half-time for the iodine in remnants is somewhat reduced, the actual dose to remnants is often much less (a remnant dose of 300 Gy is believed necessary for successful ablation (*5*)). Several studies have indicated that children receive administered activity levels in the same range as adults. A retrospective study of 40 children with thyroid cancer (mean age at treatment, 14.6 y; range, 6–20 y) found a mean level of 7.3 GBq (197 mCi) (range, 2.9–25.8 GBq) (*6*). A study of 26 children in The Netherlands with thyroid cancer (mean age at treatment, 12.5 y; range, 5–19 y) found an ^{131}I activity ranging from 2 to 8 GBq (54–216 mCi) (*7*). When thyroid cancer has metastasized, as was the case in about 50% of the cases of Chernobyl-related thyroid cancer (*8,9*),

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activities of up to 7.4 GBq (200 mCi) are recommended for the initial treatment. Oliynyk et al. (*8*) reported that the total administered activity level for thyroid ablation treatment in 249 children with thyroid cancer after the Chernobyl accident ranged from 1.3 to 22.4 GBq (35–605 mCi).

MATERIALS AND METHODS

Effective Half-Time of Iodide in Athyrotic Patients

To estimate the absorbed dose from ^{131}I ablation treatment, one must know the effective half-time of ^{131}I in athyrotic patients. The standard ^{131}I dosimetric model of the International Commission on Radiological Protection assumes that inorganic iodine is rapidly excreted from blood, with a half-time of 0.25 d (*10*). However, after thyroidectomy, patients are told to discontinue thyroid hormone replacement and to consume an iodine-restricted diet for 3–6 wk before administration of radioactive iodine. This hypothyroid state substantially increases the half-time of inorganic iodine in the body, leading to a 2- to 3-fold increase in whole-body retention of radioiodine at 48 h (*11–13*). The increased biologic half-time of iodine in patients does not appear to be significantly influenced by uptake in thyroid remnants or metastases (*13*), because these tissues typically have a substantially reduced uptake and retention of ^{131}I.

We identified 13 studies (Table 1) that estimated the mean effective half-time of ^{131}I in athyrotic patients, with sample means ranging from 0.52 to 3.9 d. Most of these studies determined the effective half-time of ^{131}I by fitting patient retention data with a single exponential function, thereby slightly underestimating the effective half-time. The data indicate that the effective half-time of iodide in athyrotic patients is log-normally distributed (*14,15*), with a mean ranging from 0.70 to 0.77 d.

A pooled analysis (sample-number weighted mean of the means) of the data in Table 1 gives a population mean effective whole-body half-time for ^{131}I in athyrotic patients of 0.75 d. The pooled SD (PSD) from k series of measurements can be calculated as

$$\mathrm{PSD} = \left(\left((n_1 - 1)s_1^2 + (n_2 - 1)s_2^2 + \ldots + (n_k - 1)s_k^2\right) \Big/ (n_1 + n_2 + \ldots + n_k - k)\right)^{1/2},$$

where n_1, n_2, …, n_k and s_1, s_2, …, s_k are the size and SD, respectively, of the individual studies. The pooled SD of the 10 studies that reported an SD is 0.37 d. Thus, the best estimate of the mean and SD of the effective whole-body half-time for ^{131}I in athyrotic patients is 0.75 ± 0.37 d. If the analysis is restricted to the 10 studies with both a mean and an SD, the best estimate is 0.76 ± 0.37 d. The mean of the last study in Table 1 lies more than 2 SDs from either of these means (0.75 or 0.76 d) and thus may not belong to the same population. If this study is excluded from the analysis, the best estimate of the mean and SD of the effective whole-body half-time for ^{131}I in athyrotic patients is 0.70 ± 0.28 d, very similar to that found in the studies of Pacilio et al. (*14*) and North et al. (*15*). In the present study, we used an effective half-time of 0.70 d in estimating dose from ^{131}I ablation treatment in athyrotic pediatric and young adult patients.

^{131}I Whole-Body and Breast Tissue Dosimetry

The OLINDA/EXM computer code (*22*) was used to estimate doses to various organs in 10-y-old, 15-y-old, and young adult females from ablation treatment. Uptake in stomach, liver, and intestines was assigned activity as in the standard model for iodide (*23*), and the remaining activity was assumed to be uniformly distributed throughout all tissues of the body and eliminated through the urinary pathway at a rate determined by the assumed whole-body effective half-time. The dynamic bladder feature of the code was used to estimate the number of disintegrations occurring in the urinary bladder. Table 2 provides estimates of breast, red marrow, and whole-body dose, assuming a total-body effective ^{131}I half-time in athyrotic patients of 0.7 d and for the extreme mean half-times listed in Table 1 of 0.5 and 1.3 d. The best estimates of the dose to the breast in 10-y-old, 15-y-old, and young adult athyrotic females are 9.8E−2, 6.2E−2, and 6.2E−2 mGy/MBq, respectively (Table 2).

These calculations did not include the cross-dose contribution to breast tissue from ^{131}I possibly taken up by thyroid remnants. Luster et al. (*5*) estimated the percentage of ^{131}I uptake and the effective half-time in thyroid remnants for 14 lesions in 9 patients. The uptake varied from about 0.3% to 1.8% at 24 h (mean, about 0.5%), and the effective half-times varied from 1.25 to 5.4 d (mean, about 4.2 d) in hypothyroid adults. A sensitivity analysis using the OLINDA/EXM code indicated that cross dose from ^{131}I in thyroid remnants may contribute from 6.6E−5 to 1.7E−3

TABLE 1
Mean Effective Half-Time of ^{131}I in Athyrotic Patients

Mean effective whole-body half-time (d)	Maximum effective whole-body half-time (d)	Number of patients	Method of determining half-time	Citation
0.52 ± 0.10	0.76	9	Blood/scanning	(*5*)
0.52 ± 0.12	0.75	14	External scanning	(*17*)
0.54 ± 0.14		163	External scanning	(*13*)
0.7 ± 0.24	2.03	265	External scanning	(*14*)
0.71	4.4	268	External scanning	(*15*)
0.71		33	External scanning	(*12*)
0.74 ± 0.033		42	External scanning	(*16*)
0.77 ± 0.57	2.1	87	External scanning	(*18*)
0.9	4.4	19	External scanning	(*15*)
0.98 ± 0.32	1.9	24	External scanning	(*19*)
1.03 ± 0.19		8	External scanning	(*20*)
1.33 ± 0.13		14	External scanning	(*16*)
3.9 ± 1.7	16	14	Blood	(*21*)

TABLE 2
Dose Estimates for ^{131}I Ablation Treatment in Female Patients

Age group	0.50-d half-time		0.70-d half-time		1.3-d half-time	
	mGy/MBq	rad/mCi	mGy/MBq	rad/mCi	mGy/MBq	rad/mCi
Adult						
Breasts	4.17E−02	1.54E−01	6.20E−02	2.29E−01	1.26E−01	4.66E−01
Red marrow	4.56E−02	1.69E−01	6.48E−02	2.40E−01	1.25E−01	4.64E−01
Total body	5.83E−02	2.16E−01	8.06E−02	2.98E−01	1.51E−01	5.58E−01
15-y-old child						
Breasts	4.18E−02	1.53E−01	6.21E−02	2.33E−01	1.26E−01	4.84E−01
Red marrow	4.69E−02	2.84E−01	6.68E−02	3.78E−01	1.29E−01	6.75E−01
Total body	5.83E−02	2.16E−01	8.05E−02	2.98E−01	1.51E−01	5.57E−01
10-y-old child						
Breasts	6.64E−02	2.46E−01	9.82E−02	3.63E−01	1.99E−01	7.35E−01
Red marrow	7.30E−02	2.70E−01	1.05E−01	3.88E−01	2.06E−01	7.60E−01
Total body	9.38E−02	3.47E−01	1.30E−01	4.80E−01	2.44E−01	1.20E+00

mGy/MBq to the breast dose. Thus, if the data of Luster et al. (*5*) are representative, ^{131}I taken up by thyroid remnants does not provide a significant cross dose to breast tissue.

RESULTS

BEIR VII (*24*) estimates that external exposure of 10-, 15-, and 20-y-old females to 0.1 Gy results in an absolute risk of 7.12E−3, 5.53E−3, and 4.29E−3, respectively, that female breast cancer will develop. Assuming that a 5.6-GBq (150 mCi) dose applied during ablation results in a breast dose ranging from 0.35 to 0.55 Gy (Table 2), thyroid ablation in pediatric or young adult females may result in a lifetime risk of breast cancer ranging from 2 to 4 cases per 100 such individuals exposed. These estimates of cancer risk may overestimate risk by a factor of up to 2 because of the possibly reduced biologic effectiveness of internal exposure to ^{131}I, compared with the external exposures received by the atomic bomb survivors (*25*).

Using a pooled analysis of 8 different studies, Preston et al. (*26*) estimated that when the breast tissue of a 22-y-old is exposed to 0.1 Gy, the risk of breast cancer developing by the age of 65 y is 5.8×10^{-3}. On the basis of atomic bomb survival data, Land et al. (*27*) estimated that exposure at the age of 10 y produces an excess relative risk of breast cancer about twice that of exposure at the age of 22 y. Assuming that exposure at the age of 10−15 y produces 2 times the risk, the estimate of Preston et al. (*26*) indicates that in approximately 5.8% of 10- to 15-y-old girls whose breast tissue is exposed to 0.5 Gy, radiation-induced breast cancer may develop by the age of 65 y—a percentage that is consistent with the above estimates.

For girls 10 and 15 y old at exposure, the lifetime risk of solid tumors from 0.1 Gy of external radiation exposure is 2.5E−2 and 1.99E−2, respectively (*24*). A 5.6-GBq (150 mCi) dose applied during ablation results in a whole-body dose of 0.7 and 0.4 Gy in 10- and 15-y-old girls, respectively. These values correspond to a lifetime risk of 17 and 8 solid tumors, respectively, per 100 such girls exposed. The lifetime risk in 10- and 15-y-old boys is 7 and 4 solid tumors, respectively, per 100 such boys exposed.

DISCUSSION

A long history of medical use has shown ^{131}I ablation to be safe and effective in the treatment of thyroid cancer. However, the Chernobyl accident was unique in that a large number of young females (most under the age of 5 y at the time of exposure) were treated with ^{131}I for thyroid cancer. The long-term medical effects of ^{131}I ablation treatment in young females are unknown.

Epidemiologic Studies

The major retrospective epidemiologic studies of women treated with ^{131}I have not shown an increased rate of breast cancer in these women. If exposure to radioactive iodine can cause breast cancer, why have these studies not detected an increase in breast cancer rates? The most probable reason, aside from the fact that therapeutic doses of radioactive iodine may not cause breast cancer, may be that most women in these studies were over the age of 50 y at the time of exposure. Epidemiologic studies of exposure of the breast to external radiation indicate that the risk of radiation-induced breast cancer is minimal after the age of 45 y (*26,28*). The studies on atomic bomb survivors showed virtually no increased risk of breast cancer in women who were more than 40 y old at the time of exposure (*29*).

Three of the major studies on ^{131}I-induced breast cancer were done by Hall et al. (*2,3*) and Franklyn et al. (*4*). The average age at treatment for patients in these 3 studies was 50, 57, and 57.1 y, respectively. The median latency period for breast cancer is about 20 y. Thus, breast cancer caused by ^{131}I administered at the age of 50 y will generally not be detectable until the age of 70 y. At the age of 70 y, background breast cancer rates are high, making it difficult to detect small increases. In a pooled analysis of 8 cohorts, Preston et al. (*26*) estimated that after a 1.0-Gy exposure at the age of 25 y, the risk of breast cancer developing by the

age of 65 y was 1.3×10^{-2}. In contrast, after a 1.0-Gy exposure at the age of 50 y, the risk of breast cancer developing by the age of 65 y was 4.8×10^{-8} and the risk by the age of 70 y was 5.2×10^{-8}. About 6.3% (6.3×10^{-2}) of women are between the ages of 50 and 70 y when breast cancer develops (*30*). Thus, it is unlikely that epidemiologic studies of women exposed to radioactive iodine after the age of 50 y will detect an increase in the incidence of breast cancer. These negative epidemiologic findings cannot be taken to demonstrate that ^{131}I administered to younger women will not cause breast cancer.

Comparison with Data on Atomic Bomb Survivors

The data on atomic bomb survivors show that the female breast is the most radiation-sensitive tissue among the tissues in which solid cancer develops. In atomic bomb survivors, the average dose to breast tissue was 0.28 Sv, with an average age at exposure of 27 y (*31*). The excess relative risk for this cohort was 1.74 at 1 Sv. The excess relative risk of breast cancer in girls 5–14 y old at the time of exposure was 2.77 per Sv (*31*).

If we assume a median total applied dose of 10.7 GBq (289 Ci) of ^{131}I for ablation treatment associated with Chernobyl (*9*), the dose to pediatric and young adult breast tissue from ^{131}I ablation treatment ranges from 0.7 to 1.0 Gy. These doses to breast tissue are 2.5−3.5 times higher than the average dose to breast tissue in atomic bomb survivors. These doses are also higher than the median Chernobyl-related doses—estimated to range from 0.2 to 0.6 Gy—to thyroid tissue in children who developed thyroid cancer (*32–34*).

CONCLUSION

Since the Chernobyl accident, thyroid cancer has developed thus far in about 4,000 children. In children who ingested ^{131}I after the Chernobyl accident and in whom thyroid cancer developed, the median dose to the thyroid was not high, appearing to range from 0.2 to 0.6 Gy (*32–34*), with statistically significant increases in thyroid cancer risk seen for exposures greater than 0.2 Gy (*34*).

Most children in whom thyroid cancer developed as a result of the Chernobyl accident received ^{131}I ablation treatment (*8*), with total administered doses generally ranging from 1.3 to 22.4 GBq (35–605 mCi) (8). However, in some cases, total administered doses reached 43.9 GBq (1.18 Ci) (9). Most of these children were between 8 and 14 y old at the time of the first treatment (*8,9,35*), and the cancer had metastasized in about 50% of them (*8,9*). Thyroid cancer often requires multiple treatments, with about 50% of the Chernobyl children receiving a total applied dose of at least 10.7 GBq (289 Ci) (*9*). Thus, the median dose to breast tissue in the Chernobyl children and young adults who received ^{131}I ablation treatment may range from 0.7 to 1 Gy. There are substantial uncertainties associated with these dose estimates, but they do indicate the need for additional investigation of the issue.

The dose to pediatric breast tissue from a single 3.7-GBq (100 mCi) ablation treatment is estimated to equal or surpass the mean dose to breast tissue in atomic bomb survivors—a dose that resulted in statistically significant increases in breast cancer risks. In addition, the average age of exposure of atomic bomb survivors was 27 y, whereas most of the children receiving ablation treatment were between 8 and 14 y old. We note that to date no increase in cancer rates has been observed among young Chernobyl women treated with ^{131}I.

Although current evidence is not conclusive regarding a possible risk of breast cancer from ^{131}I ablation treatment in young women, additional research is needed on the quantity and biologic half-time of ^{131}I taken up in the breast tissue of young women. Of particular importance is the need to determine the effective whole-body half-time of iodide in athyrotic, hypothyroid young females. In addition, increased surveillance may be needed for young female thyroid cancer patients who received ^{131}I ablation treatment. Although the benefits of thyroid cancer ablation treatment are universally recognized, radiation risks for children undergoing ^{131}I ablation treatment are not negligible. Birrell and Cheetham (*36*), in discussing ^{131}I treatment for Grave's disease in young children, noted that adequate data on the neoplastic potential of ^{131}I in children are not available and recommended long-term follow-up of all young patients receiving radioactive iodine therapy. This recommendation holds even more strongly for the Chernobyl children.

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