Iodine-131 in Breast Milk Following Therapy for Thyroid Carcinoma

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This study evaluates breast milk secretion of ^{131}I following therapeutic administration of 4000 MBq of ^{131}I-iodide during lactation. **Methods:** Breast milk ^{131}I activity concentration was measured over a 32-day period. Dosimetry calculations were undertaken to estimate the period for discontinuation of breast feeding and the equivalent dose to the breasts. **Results:** To achieve an infant effective dose <1 mSv and an infant thyroid dose <10 mSv, breast feeding would need to be discontinued for at least 52 days. The estimated equivalent dose to the breasts was 1.6 Gy. **Conclusion:** It is suggested that ^{131}I-iodide administration is not undertaken during lactation and that breast feeding is discontinued several days prior to administration.

Key Words: thyroid carcinoma; iodine-131 therapy; breast milk

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There have been few reports documenting secretion of ^{131}I into human breast milk (*1–5*). We recently had the opportunity to study breast milk secretion of ^{131}I over a 32-day period following the therapeutic administration of 4000 MBq of ^{131}I-iodide for ablation of remnant thyroid tissue after near-total thyroidectomy for follicular thyroid carcinoma.

MATERIALS AND METHODS

Patient

A 34-yr-old female noticed progressive swelling in her neck following her third pregnancy. She presented for investigation 3 mo after delivery. Ultrasound imaging demonstrated a 4-cm nodule in the left lobe of the thyroid gland. Biopsy confirmed malignancy and she underwent total thyroidectomy. Histology of the excised nodule showed a 40 × 23-mm encapsulated follicular thyroid carcinoma of microfollicular type with areas of capsular invasion and a single area of vascular invasion. Thyroxine therapy was withheld for 30 days pending ^{131}I assessment for remnant thyroid tissue and functioning metastases. At the time of assessment she was clinically hypothyroid. Laboratory evaluation revealed serum-free T4 <4 pmole/liter (normal 9–26 pmole/liter), serum TSH 110 mU/liter (normal 0.4–4.0 mU/liter) and serum thyroglobulin <1.0 μg/liter (normal 3–43 μg/liter).

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The patient was keen to resume breast feeding her infant following ^{131}I assessment and therapy if assay of breast milk ^{131}I activity indicated that it would be safe to do so. Nursing was discontinued prior to ^{131}I administration with regular extraction of milk using a breast pump to maintain lactation.

Imaging and Uptake Measurements

Whole-body imaging and thyroid uptake measurements were undertaken 48 hr after the administration of 200 MBq of [^{131}I] sodium iodide and 48 hr after the subsequent therapeutic administration of 4000 MBq of [^{131}I]sodium iodide using a gamma camera with a high-energy collimator.

Breast Milk

Breast milk was obtained at intervals following diagnostic and therapeutic ^{131}I administration. Aliquots (diluted as necessary) were counted in a through-crystal gamma counter (3-inch sodium iodide crystal; efficiency for ^{131}I counting; 36%) with appropriate standards. Iodine-131 activity in milk was expressed as Bq · ml^{-1} at the time of milk collection. The volume of milk samples was obtained by weighing (assumed density 1.03 mg · ml^{-1}).

Urine

Total ^{131}I excretion in urine over the initial 41 hr following therapeutic ^{131}I administration was calculated by sampling the pooled urine collection over this period.

Dosimetry Calculations

Discontinuation of Breast Feeding. To determine the period of discontinuation of breast feeding two criteria were examined:

1. Infant estimated effective dose <1 mSv: *ICRP Publication 61* (*6*) gives an adult annual limit for ingestion of ^{131}I as 800 kBq. This is calculated to give a 70-kg worker an annual effective dose of 20 mSv. By proportion, based on body weight (infant weight 5.5 kg at 4 mo) and assuming equality of radiosensitivity between infant and adult organs, an effective dose of 1 mSv (the recommended annual effective dose for an adult member of the general public) would be given by ingestion of 3143 Bq of ^{131}I.
2. Infant thyroid dose <10 mSv: In 1965, *ICRP Publication 9* (*7*) recommended an annual dose limit of 1.5 rem (15 mSv) to the thyroid for children under 16 yr of age. This was half the dose limit for an adult member of the general public. Following revision of dose limits in the current ICRP recommendations (*8*), no specific value is given for the young thyroid. The implied dose limit for an adult member of the general public is 20 mSv if the thyroid is the only organ irradiated. Halving this gives a value of 10 mSv for children. *NCRP Report 73* (*9*) suggests an absorbed dose to the thyroid of the neonate (thyroid mass 1.5 g, thyroid uptake 70%)

of 4.3 Gy/MBq of ^{131}I administered. Using this figure, a thyroid dose of 10 mSv would be given by ingestion of 2326 Bq of ^{131}I.

Activity Concentration to Resume Breast Feeding. Following administration of ^{131}I-iodide to a lactating mother, breast milk ^{131}I activity concentration demonstrates a biexponential decline. If breast feeding recommences during the second exponential phase, ^{131}I activity concentration will be given by the formula:

$$C = C_R e^{-\lambda t},$$

where C is breast milk ^{131}I activity concentration ($Bq \cdot ml^{-1}$); C_R is breast milk ^{131}I activity concentration at which breast feeding recommences ($Bq \cdot ml^{-1}$); λ is the decay constant of second exponential component of breast milk ^{131}I activity concentration curve (h^{-1}); and t is time after breast feeding recommences (hr).

The ^{131}I activity ingested by the infant during a feed will be given by the formula:

$$A = VC = VC_R e^{-\lambda t},$$

where A is breast milk ^{131}I activity ingested (Bq) and V is feed volume (ml).

For multiple feeds continued until breast milk ^{131}I activity is effectively zero, total ^{131}I activity ingested by the infant is given by the formula:

$$A_T = \sum_{i=0}^{\infty} V_i C_R e^{-\lambda t_i},$$

where A_T is total breast milk ^{131}I activity ingested (Bq).

Assuming feeds of equal volume at regular intervals:

$$A_T = VC_R \sum_{i=0}^{\infty} e^{-\lambda i \Gamma},$$

where Γ is the feed interval (hr).

Further assuming that ingested ^{131}I activity is completely absorbed from the infant's gastrointestinal tract, the breast milk ^{131}I activity concentration at which breast feeding can recommence is given by the formula:

$$C_R = \frac{A_T}{V}(1 - e^{-\lambda\Gamma}) = \frac{A_T}{V}\left(1 - e^{\frac{-0.693}{T_E}\Gamma_1}\right), \qquad \text{Eq. 1}$$

where T_E is the effective half-life for ^{131}I in breast milk during the second exponential component of breast milk ^{131}I activity concentration curve (hr).

Equivalent Dose to the Breasts

The lactating breast is a complex glandular structure with mammary epithelium distributed throughout the breast mass. *ICRP Publication 23* (*10*) gives total breast mass during lactation in the range 560–1800 g with 15%–43% cistern tissue. Approximately one-tenth of cistern tissue comprises mammary epithelium; the remainder is the milk-containing reservoir. Assuming an average breast mass of 1200 g with 30% cistern tissue, the mammary epithelial mass would be estimated as 36 g and the volume of the milk-containing reservoir would be 324 ml. Further assuming that ^{131}I activity concentration in the reservoir is that of expressed milk, that the breast remains full (ignoring changes of milk volume in the breast as a result of feeding) and that the volume of the milk reservoir does not change during the period of lactation, the cumulated activity in the breast can be calculated from the area under the breast milk ^{131}I activity concentration curve and the estimated milk reservoir volume.

The equilibrium dose constant for ^{131}I beta particles and internal conversion electrons is 0.110 g · Gy/MBq · hr (*11*). The average particulate dose may be estimated taking the absorbed fractions as unity and forms the major component of the total radiation dose. The equilibrium dose constant for the major gamma photon (0.364 MeV) is 0.169 g · Gy/MBq · hr and the sum of the equilibrium dose constants for other gamma photons and x-rays is 0.049 g · Gy/MBq · hr (*11*). Photon-absorbed fractions for the lactating breast as both a source and target organ are not available. An estimate has been made using the data for point and uniform sources in small spheres surrounded by a scattering medium (*12*). Cistern tissue is represented as a 180-g sphere in each breast. By extrapolation of the published absorbed fractions for uniform source distribution beyond 100 g and comparison with those for point sources at the center of spheres up to 500 g, an estimated value of 0.085 is reached at 0.364 MeV with similar values for the minor gamma photon and x-ray emissions. In the dosimetry calculation, the contributions from activity in the other breast, background activity elsewhere in the body and vascular activity within the breast are not assessed. The contribution from the 1.1% ^{131}Xe daughter radionuclide has been ignored. The absorbed dose to the breasts is given by the formula:

$$\bar{D} = \frac{\tilde{A}}{m}\sum_j \Delta_j \Phi_j, \qquad \text{Eq. 2}$$

where $\bar{D}$ is the absorbed dose to the breasts (Gy); $\tilde{A}$ is the cumulated activity in the breast (MBq · hr); m is the mass of breast tissue (g); Δ_j is the equilibrium dose constant for j^{th} radiation (g · Gy/MBq · hr); and Φ_j is the absorbed fraction for j^{th} radiation.

With a radiation weighting factor of 1, this becomes the equivalent dose to the breasts (Sv).

RESULTS

Imaging after administration of 200 MBq of [^{131}I]sodium iodide showed two areas of uptake in the neck presumed to be remnant thyroid tissue. Forty-eight-hour ^{131}I uptake in these areas was calculated as 0.8% of the administered dose. Imaging after administration of 4000 MBq of [^{131}I] sodium iodide showed the two areas of uptake in the neck and prominent uptake in the lactating breasts (Fig. 1). There were no features to suggest functioning metastases of thyroid carcinoma. Forty-eight-hour ^{131}I uptake in the neck was calculated as 0.08% of the administered dose.

Extraction of breast milk was undertaken up to five times each day. The average milk volume was 202 ml/24 hr (range 0–560 ml/24 hour). Figure 2 shows ^{131}I activity concentration in breast milk. Assuming a monoexponential decline of ^{131}I activity concentration over the initial 48 hr following administration of 200 MBq of [^{131}I]sodium iodide the effective half-life is calculated as 0.54 days. Following administration of 4000 MBq of [^{131}I]sodium iodide the de-

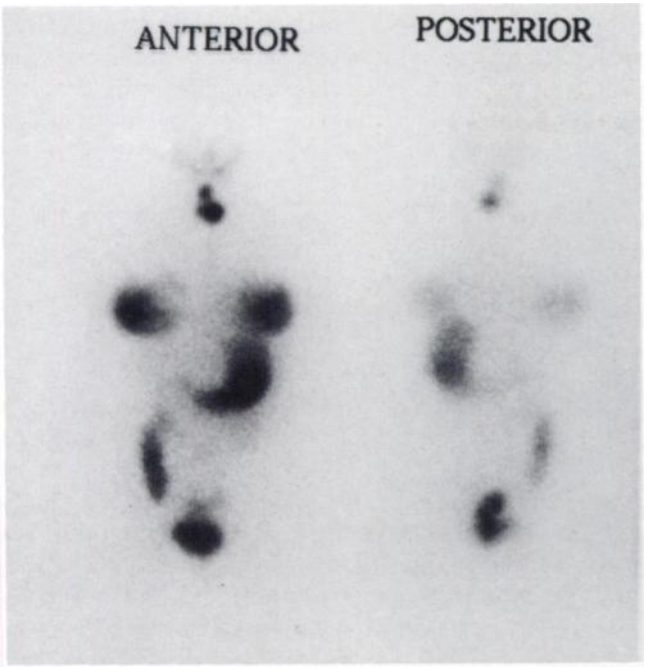

FIGURE 1. Anterior and posterior whole-body images showing prominent ^{131}I activity in lactating breasts.

cline of ^{131}I activity concentration appears biexponential. Least-squares regression indicates effective half-lives of 0.44 and 4.4 days (biological half-lives 0.47 and 9.8 days). Assuming a linear increase of breast milk ^{131}I activity concentration from the time of administration of 4000 MBq of [^{131}I]sodium iodide to the time of the initial breast milk sample, and extrapolating the activity concentration curve to infinity, the cumulated activity concentration (area under curve) is calculated as 45.2 MBq · hr/ml. Table 1 shows the distribution of ^{131}I activity 41 hr after administration of 4000 MBq of [^{131}I]sodium iodide. Table 2 shows the proportion of cumulated activity in breast milk at various times after administration of 4000 MBq of [^{131}I]sodium iodide.

The breast milk ^{131}I activity concentration at which breast feeding can resume is calculated using Equation 1.

TABLE 1
Distribution of ^{131}I Activity 41 Hours After Therapeutic [^{131}I]Sodium Iodide (4000 MBq)

Source	Activity (MBq)	% administered dose (%)
Urine	2275.6	65.8
Milk	878.9	25.4
Thyroid	24.1	0.08
Residual	301.4	8.72
Total	3456.0	100.0

Assuming regular feeds at 4-hr intervals and equal feed volumes of 250 ml (1500 ml milk daily), the breast milk ^{131}I activity concentration is 0.33 Bq/ml^{-1} (Day 50 following therapy) for infant effective dose <1 mSv and 0.24 Bq/ml^{-1} (Day 52) for infant thyroid dose <10 mSv. Assuming equal feed volumes of 140 ml (840 ml milk daily) the corresponding figures are 0.58 Bq/ml^{-1} (Day 46) for infant effective dose <1 mSv and 0.43 Bq/ml^{-1} (Day 48) for infant thyroid dose <10 mSv.

The equivalent dose to the breasts is calculated using Equation 2. Assuming a milk reservoir volume of 324 ml and breast mass of 1200 g, the absorbed dose to the breasts is 1.6 Gy.

DISCUSSION

Following ingestion of ^{131}I-iodide there is almost complete absorption from the gastrointestinal tract. In the euthyroid individual, 18%–25% of the administered activity is taken up by the thyroid gland, incorporated into thyroid iodoproteins and subsequently released into the blood as thyroid hormone. Small amounts of ^{131}I-iodide are taken up by salivary glands, gastric mucosa, choroid plexus, ciliary body and sweat glands. The remainder of the administered activity is excreted into the urine (*13*). In the absence of the thyroid gland there is no incorporation of ^{131}I-iodide into thyroid iodoproteins and virtually all of the administered dose is excreted into the urine. During lactation, the mammary glands actively secrete iodide establishing a substantial concentration gradient between plasma and milk.

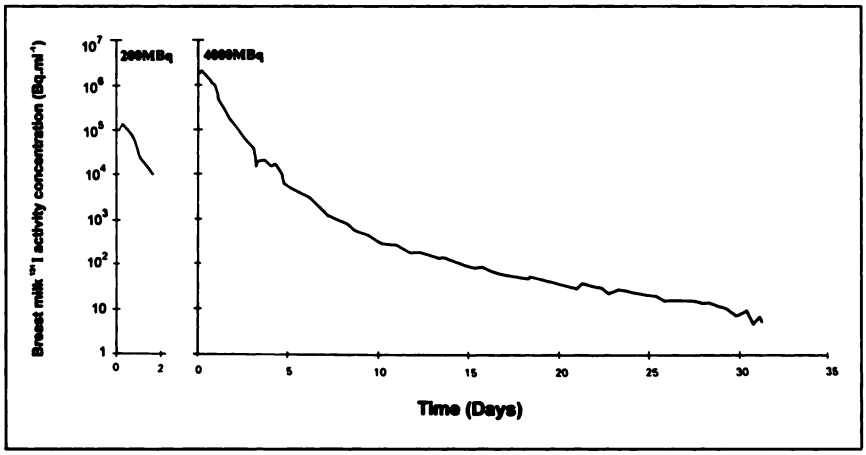

FIGURE 2. Breast milk ^{131}I activity concentration following administration of 200 MBq and 4000 MBq [^{131}I]sodium iodide.

TABLE 2
Cumulated ^{131}I Activity Concentration in Breast Milk After Therapeutic [^{131}I]Sodium Iodide (4000 MBq)

Time following ^{131}I (days)	Cumulated breast milk ^{131}I activity concentration (MBq · hr/ml)	(%)
0.5	25.2	55.7
1.0	34.5	76.3
2.0	42.8	94.6
7.0	45.1	99.8
Total	45.2	100.0

The only published report documenting ^{131}I-iodide secretion into human breast milk in the presence of severe hypothyroidism involved breast milk sampling for 4 days after administering 185 MBq of [^{131}I]sodium iodide (*4*).

In our study, breast milk sampling continued for 32 days by which time daily milk volumes were low and it was evident that a further period of discontinuation of breast feeding was required. Sampling was discontinued and hopes to resume breast feeding abandoned.

Forty-one hours after administration of 4000 MBq of ^{131}I-iodide, 91.28% of the administered activity had been recovered: 65.8% in urine, 25.4% in breast milk. This suggests that 27.9% of the total administered activity would be secreted into breast milk.

The decline of breast milk ^{131}I activity concentration appears to be biexponential and uninfluenced by the volume of breast milk extracted or by feed intervals although total ^{131}I activity secreted in breast milk will depend on the volume of breast milk extracted. The rapid initial decline reflects clearance of ^{131}I-iodide by the breast and kidneys. The slower subsequent decline presumably reflects clearance of ^{131}I-iodide recirculating following metabolism of thyroid iodoproteins and thyroid hormone (*14*) produced by remnant thyroid tissue under intense TSH stimulation.

The single published study with prolonged sampling of breast milk after ^{131}I-iodide administration involved a patient with Graves' disease (thyroid uptake 44% at 48 hr) given 355.2 MBq of ^{131}I-iodide. A biexponential decline of breast milk ^{131}I activity concentration was demonstrated with effective half-lives 0.46 and 5.9 days (biological half-lives 0.49 and 21.9 days) (*5*). The longer half-life for the second exponential component presumably reflects the substantial incorporation of ^{131}I-iodide into thyroid iodoproteins in this hyperthyroid patient.

An acceptable dose to an infant as a result of ingestion of ^{131}I-iodide in breast milk is a matter for debate. An infant effective dose <1 mSv has been suggested as a guideline for determination of the period for interruption of breast feeding following radiopharmaceutical administration (*15*) and this would agree with recommendations for limits of public exposure to radiation (*ICRP Publication 60*) (*8*). The infant effective dose has been calculated from the adult effective dose using body weight ratio (5.5-kg infant-to-70 kg adult). In fact, total body absorbed dose increased with body weight at a slower rate than this ratio (*9*) and infants may excrete radiopharmaceuticals at a faster rate than adults. An infant thyroid dose <10 mSv is based on the dose limit to the thyroid for children under 16 yr of age. Both criteria produce similar requirements for the period of discontinuation of breast feeding (50/52 days for daily milk ingestion of 1500 ml; 46/48 days for daily milk ingestion of 840 ml). These periods are broadly in agreement with previous recommendations (*16,17*). The infant will also receive some radiation exposure from the mother as a result of handling and nursing.

ICRP Publication 53 (*18*) gives an absorbed dose to the nonlactating breasts (thyroid blocked-uptake 0%) as 3.3×10^{-2} mGy/MBq of ^{131}I-iodide ingested. Following therapeutic administration of ^{131}I-iodide (4000 MBq) the estimated absorbed dose to the breasts would be 0.13 Gy. In the current study the calculated absorbed dose to the lactating breasts is 1.6 Gy.

Calculation of the absorbed dose to maternal breast tissue during lactation involves a number of simplifying assumptions. We have assumed average breast mass (1200 g) and cistern tissue (30%) (*10*). The cumulated activity in the breast is calculated as the product of the area under the breast milk ^{131}I activity concentration curve (45.2 MBq · hr/ml) and milk reservoir volume (324 ml). This assumes that ^{131}I is only present in breast milk and not elsewhere in breast tissue. No allowance is made for any effects due to partial emptying and subsequent refilling of the breasts with each feed. Modeling the breasts using small spheres surrounded by scattering tissue will overestimate the absorbed photon dose to the breast tissue. It is also assumed that both breast milk and mammary secretory epithelium are distributed uniformly throughout breast tissue. This inevitably represents a substantial oversimplification in terms of microdosimetry.

Cumulated breast milk ^{131}I activity builds up very rapidly after ^{131}I administration: 55.7% at 12 hr; 76.3% at 24 hr; and 94.6% at 48 hr. Discontinuation of breast feeding immediately before ^{131}I administration would result in a significant absorbed dose to breast tissue and breast feeding should be discontinued several days before administration to ensure that iodide secretion into milk has ceased and to minimize the absorbed dose to breast tissue.

In the derivation of organ-weighting factors, *ICRP Publication 60* (*8*) uses a value of 0.2%/Sv as the probability coefficient for induction of fatal breast cancer at some time following irradiation. The estimated equivalent dose to the breasts (1.6 Sv) would give a probability for induction of fatal breast cancer of 0.32%. This value includes the whole age range and would be an overestimate for an individual at age 34.

Studies of breast cancer risk following multiple x-ray exposure and external-beam therapy suggest that the relative risk is highest in patients under age 20 at the time of exposure but exposure at all ages carries some risk. The minimum latent period is in the range of 5–10 yr. The latent period may be influenced by hormonal or other age-related

factors but is unrelated to dose. There is evidence to suggest excess breast cancer risk up to maximum follow-up (30–45 yr) with no evidence that risk decreases with time after reaching some maximum value (*19*). Published data are compatible with a linear dose-response relationship although other dose-response relationships are not excluded (*19,20*). A decrease in breast cancer risk following large exposures (estimated absorbed dose >4 Gy) has been documented raising the possibility of a cell-killing effect at higher doses (*20*). Following low-dose radiation exposure, the increase in the relative risk of breast cancer is calculated as 0.42% ± 0.15%/0.01 Gy (*19*). The estimated absorbed dose to the breasts (1.6 Gy) would increase the relative risk to 1.67.

There are no published data which convincingly demonstrate a link between ^{131}I ingestion and breast cancer incidence. Epidemiological studies have shown an increased incidence of breast cancer following the diagnosis of primary thyroid cancer (*21,22*). These studies have postulated a common underlying cause but have not suggested any relationship to therapy. Follow-up studies of patients with hyperthyroidism have not demonstrated a significantly increased risk of breast cancer in those given ^{131}I therapy (*23,24*). In a study of patients with thyroid cancer given ^{131}I therapy (mean dose 4551 MBq) the estimated absorbed dose to the breasts was in the range of 0.1–0.6 Gy and the standardized incidence ratio for breast cancer was 0.9 (*25*).

During pregnancy there is a substantial increase in the mammary epithelial cell population in preparation for lactation. When lactation ceases, the mammary epithelial cell population is reduced to the resting level by cellular autolysis and macrophage activity (*26*). When the breast is irradiated during lactation, a large proportion of the exposed cells will be lost during involution. The implications of this for subsequent cancer risk are uncertain.

CONCLUSION

This study suggests that ^{131}I-iodide should not be administered during lactation. It is impractical to contemplate the resumption of breast feeding since the period for discontinuation of breast feeding is excessive even in the absence of functioning thyroid tissue. Estimation of breast dosimetry is complex but it is probable that mammary epithelial tissue receives a significant radiation dose in this situation. Breast feeding should be discontinued several days prior to ^{131}I-iodide administration to ensure that mammary secretory activity has ceased.

REFERENCES

1. Nurnberger CE, Lipscomb A. Transmission of radioiodine (I^{131}) to infants through human maternal milk. *JAMA* 1952;150:1398–1400.
2. Miller H, Weetch RS. The excretion of radioactive iodine in human milk. *Lancet* 1955;ii:1013.
3. Weaver JC, Dobson RL. Excretion of radioiodine in human milk. *JAMA* 1960;173:872–875.
4. Spencer RP, Spitznagle LA, Karimeddini MK, Hosain F. Breast milk content of ^{131}I in a hypothyroid patient. *Nucl Med Biol Int J Radiat Appl Instrum Part B* 1986;13:585.
5. Dydek GJ, Blue PW. Human breast milk excretion of iodine-131 following diagnostic and therapeutic administration to a lactating patient with Graves' disease. *J Nucl Med* 1988;29:407–410.
6. International Commission on Radiological Protection. Annual limits on intake of radionuclides by workers based on the 1990 recommendations. *ICRP Publication 61*. Annals of the ICRP, vol. 21, no. 4. Oxford: Pergamon Press; 1991.
7. International Commission on Radiological Protection. Recommendations of the ICRP. *ICRP Publication 9*. Oxford: Pergamon Press; 1965.
8. International Commission on Radiological Protection. 1990 Recommendations of the ICRP. *ICRP Publication 60*. Annals of the ICRP, volume 21, no. 1–3. Oxford: Pergamon Press; 1991.
9. National Council on Radiation Protection and Measurement. Protection in nuclear medicine and ultrasound diagnostic procedures in children. *NCRP Report 73*. Bethesda, MD: NCRP; 1983.
10. International Commission on Radiological Protection. Report of the task group on reference man. *ICRP Publication 23*. Oxford: Pergamon Press; 1975.
11. International Commission on Radiological Protection. Radionuclide transformations—energy and intensity of emissions. *ICRP Publication 38. Annals of the ICRP, volumes 11–13*. Oxford: Pergamon Press; 1983.
12. Ellett WH, Humes RW. Absorbed fractions for small volumes containing photon-emitting radioactivity. *MIRD Pamphlet no. 8*. New York: Society of Nuclear Medicine; 1971.
13. Taurog A. Hormone synthesis: thyroid iodine metabolism. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's the thyroid: a fundamental and clinical text*, 6th edition. Philadelphia: JB Lippincott Company; 1991:51–97.
14. Berson SA, Yalow RS. Quantitative aspects of iodine metabolism. The exchangeable organic iodine pool and the rates of thyroidal secretion, peripheral degradation and fecal excretion of endogenously synthesised organically bound iodine. *J Clin Invest* 1954;33:1533–1552.
15. Mountford PJ, Coakley AJ. A review of the secretion of radioactivity in human breast milk: data, quantitative analysis and recommendations. *Nucl Med Commun* 1989;1:15–27.
16. International Commission on Radiological Protection. Protection of the patient in nuclear medicine. *ICRP Publication 52*. Annals of the ICRP, volume 17, no. 4. Oxford: Pergamon Press; 1987.
17. Romney BM, Nickoloff EL, Esser PD, Alderson PO. Radionuclide administration to nursing mothers: mathematically derived guidelines. *Radiology* 1986;160:549–554.
18. International Commission on Radiological Protection. Radiation dose to patients from radiopharmaceuticals. *ICRP Publication 53*. Annals of the ICRP, volume 18. Oxford: Pergamon Press; 1987.
19. Boice JD, Land CE, Shore RE, Norman JE, Tokunaga M. Risk of breast cancer following low-dose radiation exposure. *Radiology* 1979;131:589–597.
20. Shore RE, Hempelmann LH, Kowaluk E, et al. Breast neoplasms in women treated with x-rays for acute post-partum mastitis. *J Natl Cancer Inst* 1977;59:813–822.
21. Ron E, Curtis R, Hoffman DA, Flannery JT. Multiple primary breast and thyroid cancer. *Br J Cancer* 1984;49:87–92.
22. Teppo L, Pukkala E, Saxen E. Multiple cancer: an epidemiologic exercise in Finland. *J Natl Cancer Inst* 1985;75:207–217.
23. Hoffman DA, McConahey WM. Breast cancer following iodine-131 therapy for hyperthyroidism. *J Natl Cancer Inst* 1983;70:63–67.
24. Goldman MB, Maloof F, Monson RR, Aschengrau A, Cooper DS, Ridgway EC. Radioactive iodine therapy and breast cancer. *Am J Epidemiol* 1988; 127:969–980.
25. Hall P, Holm L-E, Lundell G, et al. Cancer risks in thyroid cancer patients. *Br J Cancer* 1991;64:159–163.
26. Russo J, Russo IH. Development of the human mammary gland. In: Neville MC, Daniel CW, eds. *The mammary gland: development, regulation and function*. New York: Plenum Press; 1987:67–93.