

Radioiodine Breast Uptake in Nonbreastfeeding Women: Clinical and Scintigraphic Characteristics

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We studied the scintigraphic and associated clinical characteristics of radioiodine breast uptake in nonbreastfeeding thyroid cancer patients undergoing routine whole-body radioiodine scanning. **Methods:** We performed a retrospective review of the radioiodine scans and medical records of 30 prospectively collected cases. **Results:** Twenty-three nonpregnant patients had discontinued breastfeeding for a mean of 11.4 mo. Three postmenopausal and four single nulliparous patients had radioiodine breast uptake on one or more occasions. This represented about 6% of all female patients who had radioiodine scans over a 3-yr period. Four patterns of uptake, full, focal, crescentic and irregular, were observed. Breast uptake mimicked lung metastasis in nine patients. Expressible galactorrhea and moderately elevated prolactin levels were present in 48% and 24%, respectively, of patients examined. In 14 patients followed for an average of 11.4 mo, there were no consistent changes in the pattern or intensity of breast uptake. In 18 patients who had both ^{123}I diagnostic and ^{131}I postablation scans within a few days, breast uptake was present on both scans in 75%. In four patients, breast uptake was present, despite the 4%–9% radioiodine uptake by the thyroid; in one patient, iodinated contrast material blocked the uptake of the thyroid gland but not of the breast. **Conclusion:** Although the mechanisms of radioiodine breast uptake remain unclear, breast uptake should be suspected in all female patients with radioiodine uptake in the chest area, even in the absence of a history of breastfeeding.

Key Words: radioiodine scan; breast uptake; breastfeeding; prolactin

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Radioiodine, used routinely in the diagnosis and treatment of differentiated thyroid cancer, is known to be taken up by the lactating breast (1–4). Radioiodine uptake by the nonlactating breast, however, is not well recognized (5). Breast uptake of radioiodine can be readily distinguished from thyroid cancer metastases to the lung by its characteristic appearance, by obtaining posterior and/or lateral views of the chest or by observing a shift in the site of maximum concentration of radioiodine when the position of the breast is altered manually (5). Breast uptake, however, may be misinterpreted as lung metastases from differentiated thyroid cancer if it presents with an atypical pattern and/or is clinically unexpected.

We studied the prevalence and characteristics of radioiodine breast uptake in nonbreastfeeding patients with differentiated thyroid cancer. Since radioiodine is excreted in breast milk (6–8), the production of which is under the positive influence of prolactin (9), we also examined the prevalence of galactorrhea and elevated prolactin levels in these patients. Further, possible changes in the pattern and relative intensity of breast uptake over time, and possible differences in breast uptake between ^{123}I diagnostic and ^{131}I postablation scans, were also studied.

METHODS

Patients

All female patients with differentiated thyroid cancer who had breast uptake on radioiodine scans during a 3-yr period (January 1990 to December 1992) were prospectively identified. Their radioiodine scans and medical records were retrospectively reviewed. In our center, a questionnaire about breastfeeding, pregnancy and the date of the last menstrual period as well as measurement of TSH, free T4, thyroglobulin levels and plasma β -hCG screening test are routinely obtained prior to the administration of radioiodine in all female patients. All patients had a TSH ≥ 30 mU/liter, free T4 < 6 pmole/liter and a negative plasma β -hCG pregnancy test. Patients who had radioiodine breast uptake on scans obtained within 2 mo of terminating breastfeeding were excluded from this study.

Whole-body Imaging

Whole-body radioiodine scans were obtained after withdrawal of thyroxine therapy for 4 wk, using a large field of view gamma camera and appropriate collimation (medium-energy for ^{123}I , high energy for ^{131}I) for 300,000 counts or 10 min. Six spot images, including a posterior chest view, were obtained 24 hr after administration of 185 MBq (5 mCi) ^{123}I for diagnostic scans and about 3 days after oral administration of a ^{131}I therapeutic dose for postablation scans (when the exposure rate is < 1.8 mR/hr at 3 ft).

Semiquantitative Analysis

Because breast uptake of radioiodine was not quantitated, we related the intensity of breast uptake to that of residual thyroid tissue (or salivary glands if all thyroid tissue was previously ablated) on the same scan to semiquantitate it for follow-up comparison (^{123}I diagnostic to ^{123}I diagnostic scans without intervening treatment) and for ^{123}I diagnostic scan to ^{131}I postablation scan comparison. The following scale was used: +: minimal thyroid uptake; ++: moderate thyroid uptake; and +++: marked thyroid uptake.

TSH (normal range: 0.2–5.0 mU/liter), thyroglobulin (normal range: 2–70 $\mu\text{g/liter}$), prolactin (normal range: 4.6–38 $\mu\text{g/ml}$) and free T4 (normal range: 10–25 pmole/liter) assays were performed according to the manufacturer's recommendations.

RESULTS

During a 3-yr period, a total of 2000 scans (diagnostic and postablation) were performed in our center. Since 72% of our patients with differentiated thyroid cancer are women and an average patient is scanned at least once a year (including diagnostic and postablation scans), it is estimated that about 480 (or less) female patients were scanned during this time frame. Of these, 23 nonpregnant patients had radioiodine breast uptake despite not having breastfed, when they first presented, for an average of 11.4 mo (Table 1). In addition, radioiodine breast uptake was seen in four single nulliparous patients and in three postmenopausal patients who did not breastfeed for more than 13 yr (Table 2). Thus, radioiodine breast uptake in the absence

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TABLE 1
Clinical and Scintigraphic Findings in 23 Nonbreastfeeding Women with Radioiodine Breast Uptake

Prolactin level	No. of patients	Age (yr)	No breastfeeding (mo)*	Galactorrhea (%)	Scintigraphic pattern of breast uptake (%)				
					FU	FO	IR	CR	NE
Normal	11	35 (24-44)	13.1 (2-72)	56 [†]	50	18	27	0	5 [‡]
Elevated	4	31 (29-35)	7 (5-11)	75	62.5	25	0	12.5	0
Unavailable	8	35 (19-46)	11.1 (3-26)	33 [†]	19	62.5	6	12.5	0

*On first presentation (average 11.4 mo).

[†]Two patients were not examined for expressible galactorrhea.

[‡]One patient had a unilateral breast uptake.

Data are presented as the mean (range). Mean prolactin level was 20.3 (6-34) and 69 (41-95) $\mu\text{g/ml}$ in the normal and elevated groups, respectively. FU = full, FO = focal, IR = irregular, CR = crescentic, NE = negative.

of breastfeeding could be expected in at least 6% of hypothyroid female patients with differentiated thyroid cancer.

Patterns of Radioiodine Breast Uptake

As shown in Table 1, four patterns of breast uptake, full, focal, crescentic and irregular, similar to those reported in the lactating breast (10), were observed (Figs. 1-5). Two patients, a 32-yr-old who stopped breastfeeding for 4 mo and a postmenopausal patient (Patient 5, Table 2), had unilateral (right) breast uptake.

In most patients, the pattern and location (e.g., being lateral to the torso) of radioiodine uptake by the breast were characteristic. In eight patients, however, breast uptake was irregular and mimicked lung metastases (Fig. 1A). Lung metastases were ruled out by examining the posterior chest views that showed no activity and normal chest radiographs. In addition, in a 35-yr-old woman, the combined picture of bilateral breast uptake and focal residual stomach activity was difficult to distinguish from lung metastases (Fig. 2C). That the uptake is in the stomach was suggested from comparing the scan (Fig. 2C) to a previous scan (Fig. 2B). Furthermore, a posterior view of the chest showed no activity, chest radiograph was normal and the thyroglobulin level was undetectable. In another 29-yr-old patient, breast uptake coexisted with a focus of lung metastasis (Fig. 3). In this patient, the thyroglobulin level was 30 $\mu\text{g/liter}$ (with the only other uptake being in the thyroid bed and measuring <1%) and a lateral chest view (not shown) revealed clear separation of the focus from stomach activity (being posterior to the stomach). In

four patients with insignificant residual thyroid uptake ($\leq 1\%$), thyroglobulin levels were 8.8, 18, 86, and 95 $\mu\text{g/liter}$, respectively, initially suggesting that the uptake in the chest area represented metastatic thyroid foci. The negative posterior chest views and chest radiographs and the typical appearance of breast uptake confirmed that the uptake was in fact related to the breast and that thyroglobulin was most likely secreted by scan-negative microscopic thyroid foci.

Associated Expressible Galactorrhea and Prolactin Level

Twenty-one patients were examined for expressible galactorrhea, whereas 17 patients had their prolactin level measured by scan findings. Galactorrhea was present in 10/21 (48%) patients. As shown in Table 1, the elevation of the prolactin level, when present, was mild to moderate (up to 2.5 times upper normal level). This elevation is most likely secondary to the hypothyroid state (9,11,12). In three patients with elevated prolactin levels, pituitary images were obtained which showed partially empty sella in one patient and normal pituitary in the others. Furthermore, prolactin levels were subsequently measured in two patients while on L-thyroxine treatment; these levels became normal.

There were no consistent differences in the patterns of breast uptake in patients with normal prolactin levels compared to those with elevated prolactin levels (Table 1). Furthermore, in three patients, treatment with bromocriptine (up to 7.5 mg twice a day for 2 mo) did not result in a consistent change in the pattern or relative intensity of breast uptake, suggesting that

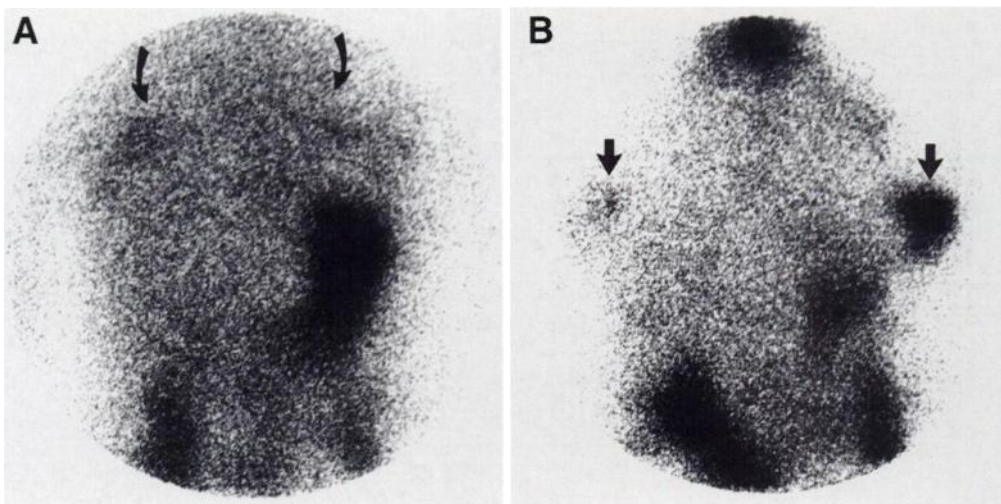
TABLE 2
Radioiodine Breast Uptake in Single Nulliparous and Postmenopausal Patients

Patient no.	Age (yr)	Last breastfeeding (yr)	Pattern/Intensity	
			Right	Left
Single				
1	25	Never	Full/++	Full/++
2	24	Never	Full/++	Full/++
3	25	Never	Full/+	Full/+
4	33	Never	Full/+	Full/+
Postmenopausal				
5	52	13	Full/+	Negative
6	59	26	Full/++	Full/++
7	55	27	Crescentic/++	Full/++

Patients 1 and 5 had a negative examination for galactorrhea and normal prolactin levels of 32 and 25 $\mu\text{g/ml}$, respectively. The intensity of breast uptake was semiquantitated by relating it to the intensity of thyroid (or salivary glands) uptake on the same scan.

+ = minimal uptake; ++ = moderate uptake.

FIGURE 1. (A) Iodine-123 diagnostic scan. Anterior chest view obtained 3 mo after discontinuation of breastfeeding. Curved arrows delineate +, irregular breast uptake, bilaterally, mimicking lung metastasis. (B) Anterior view of the chest of ^{131}I (5550 MBq) postablation scan in the same patient obtained 6 days later. Arrows delineate +++, full uptake in the left breast and +, focal uptake in the right breast. Breast uptake is more prominent in (B) than in (A) and the uptake is now lateral to the torso, confirming its presence in the breasts rather than in the lungs.



prolactin may not play a primary role in radioiodine breast uptake in this group of patients. Moreover, patterns of breast uptake were similar among the 10 patients with expressible galactorrhea (50% full, 25% focal, 10% crescentic, 15% irregular), 11 patients without expressible galactorrhea (32% full, 50% focal, 4.5% crescentic, 9% irregular, 4.5% negative) and 9 patients not examined for expressible galactorrhea (67% full, 5.5% focal, 5.5% crescentic, 17% irregular, 5.5% negative).

Breast Uptake on Follow-up Scans

In 14 patients, follow-up ^{123}I diagnostic scans were available 2–31 mo (mean 11.4) after the initial ^{123}I diagnostic scan without intervening radioiodine therapy (Table 3). One patient's scan was negative for breast uptake; this patient had been followed for 5 mo. The remaining scans did not show consistent changes in uptake pattern or relative intensity. On some scans, there was a relative decrease in breast uptake over time (Fig. 2), whereas on others the opposite was found, suggesting that breast uptake of radioiodine may not be directly related to the time elapsed since previous breastfeeding.

Comparison of Iodine-123 Diagnostic Scans to Iodine-131 Postablation Scans

Since the resolution of ^{123}I scans may be different than that of ^{131}I scans and breast uptake on the relatively early ^{123}I images (obtained at 24 hr as opposed to about 72 hr for ^{131}I images) may represent blood-pool activity, we compared the results of the two scans in 18 patients who had both scans within a few days of each other. The therapeutic ^{131}I dose ranged from 4403 to 7141 MBq (119–193 mCi). Each patient's scans were studied by an examiner blinded to their relationship. As shown in Table 4, seven breasts were ^{123}I scan-negative and ^{131}I scan-positive, whereas two breasts were ^{123}I scan-positive and ^{131}I scan-negative. Figures 1 and 4 depict examples of the discrepancy in the patterns of breast uptake between ^{123}I diagnostic and ^{131}I postablation scans. There was, however, total agreement on the pattern and relative intensity of the uptake on the two scans in 44% and 42% of breasts, respectively. Thus, there was no consistent difference in radioiodine breast uptake between the two types of scans. The dose nor the radioiodine isotope nor the scanning time appeared to be important factors in radioiodine breast uptake.

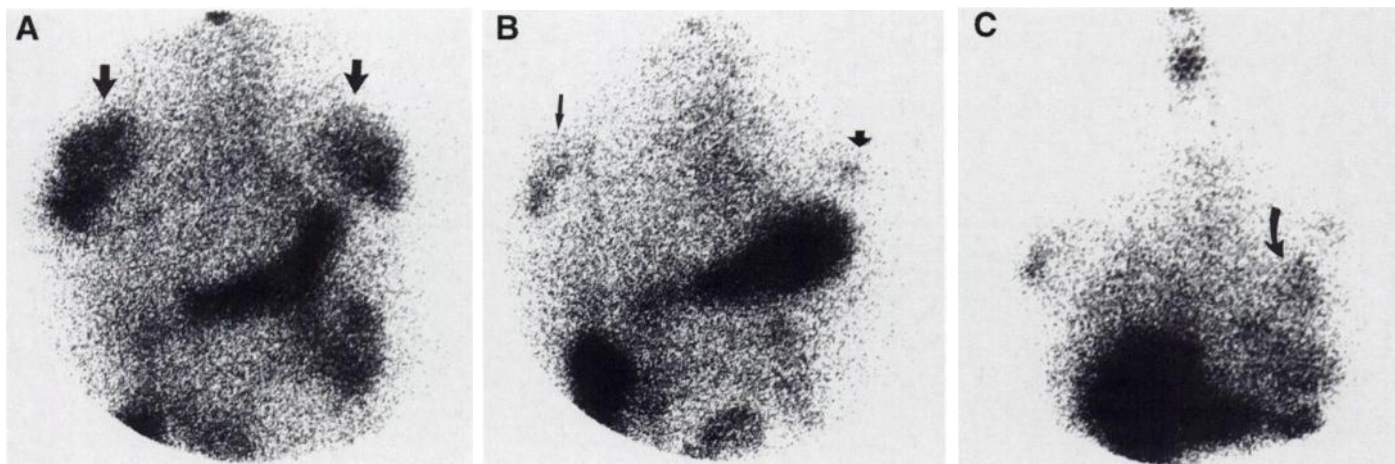


FIGURE 2. (A) Iodine-123 diagnostic scan. Anterior chest view obtained 6 mo after discontinuation of breastfeeding. Arrows delineate +++, full, in (A) breast uptake bilaterally. (B) Anterior view of the chest of ^{123}I diagnostic scan in the same patient obtained 9 mo after the scan. Arrowhead delineates +, focal uptake in the left breast and the arrow delineates ++, full uptake in the right breast. (C) Iodine-123 diagnostic scan. Anterior chest view obtained 3 mo after the scan in (B). The curved arrow delineates faint stomach activity that together with bilateral +, focal breast uptake, which persisted for 1 yr, mimicking lung metastases.

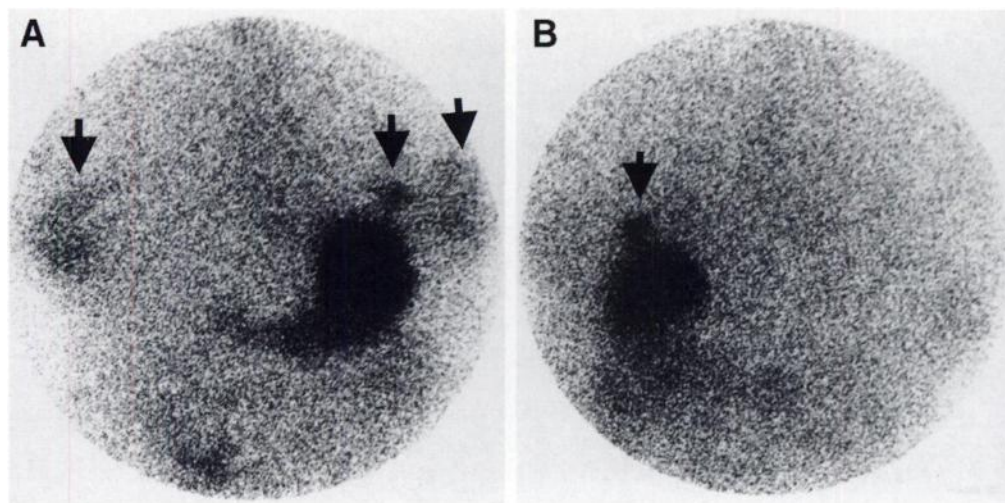


FIGURE 3. (A) Iodine-123 diagnostic scan. Anterior chest view obtained 6 mo after discontinuation of breastfeeding. Left arrow delineates +++, crescentic uptake in the right breast. Right arrow delineates ++, full uptake in the left breast. Middle arrow delineates focal lung metastasis that coexisted with the breast uptake. (B) Posterior view of the chest of the same scan. Arrow delineates focal uptake in the left lower lobe of the lung just above the stomach activity.

High Capacity of Radioiodine Breast Uptake

CT was inadvertently performed 5 days after the diagnostic scan and just before administration of the therapeutic dose of ^{131}I in one patient. As shown in Figure 5, the iodinated contrast material blocked thyroid uptake of radioiodine but not that of the breast, suggesting that the breast has a relatively large capacity for iodine uptake (or rapid turnover of iodine) and is not saturable under these circumstances. In four other patients, breast uptake was seen despite the presence of significant (4%–9%) thyroid uptake.

DISCUSSION

We recently described the patterns of breast uptake on radioiodine scans obtained within 1 wk from cessation of breastfeeding (10). In this study, we report the scintigraphic and clinical characteristics of radioiodine breast uptake in the absence of recent breastfeeding. We estimate that radioiodine breast uptake may be present on at least one occasion in about 6% of nonbreastfeeding hypothyroid female patients with differentiated thyroid cancer. The patterns of radioiodine breast uptake are similar in the presence (10) or absence of breastfeeding (Tables 1, 2) and can be classified as “full,” “focal,” “crescentic” and “irregular.”

The mechanism(s) of breast uptake of radioiodine remains unclear. Radioiodine is known to be excreted in breast milk (6–8), the production of which is regulated by prolactin (9). Thus, radioiodine breast uptake is common in the early postpartum period and during lactation: two conditions associated with elevated prolactin levels. Prolactin levels may also be

raised by various drugs (13–15), breast stimulation (16,17), hypothyroidism (9,11,12) and prolactinoma (9,18). Furthermore, galactorrhea can be associated with increased tissue sensitivity to normal prolactin levels (19). Therefore, we examined the association between radioiodine breast uptake and the presence of galactorrhea and elevated prolactin levels. Our study argues against a primary role of prolactin in radioiodine breast uptake in non-breastfeeding women. First, expressible galactorrhea was absent in 52% of patients, and prolactin levels were normal in 76% and mildly to moderately elevated in 24% of patients. Second, treatment with bromocriptine, which is expected to lower prolactin levels, did not consistently affect the pattern or intensity of breast uptake (although only a few patients were studied). Moreover, sensitization of breast tissue to prolactin due to previous periods of prolonged lactation is also not a likely explanation for breast uptake in our patients because there were no consistent changes in the pattern or relative intensity of breast uptake after a mean follow-up period of 11.4 mo. Furthermore, breast uptake was present in three postmenopausal women who had last breastfed more than 13 yr ago and in four single nulliparous women who had never breastfed.

That radioiodine breast uptake may represent blood-pool activity in the breast is also not likely because there were no consistent differences in breast uptake between ^{123}I diagnostic and ^{131}I postablation scans obtained 1 and 3 days, respectively, after radioiodine administration.

Interestingly, previous studies have related radioiodine uptake by the breast to dysplastic or neoplastic breast disease and

TABLE 3
Clinical and Scintigraphic Findings in 14 Patients with Radioiodine Breast Uptake Followed for 11.4 Months*

	Galactorrhea (%)	Prolactin ($\mu\text{g}/\text{ml}$)	Scintigraphic pattern of breast uptake (%)					Intensity of breast uptake		
			FU	FO	CR	IR	NE	+	++	+++
Initial	75 [†]	45 (15–95) [§]	61	25	3.5	10.5	0	28.6	60.7	10.7
Follow-up	57 [‡]	45 (34–68) [§]	61	21	0	11	7 [¶]	32	57	4

*Time of follow-up ranged from 2 to 31 mo. Data are presented as mean (range).

^{†‡§}Data available in eight, seven and six patients, respectively.

[¶]One patient had no breast uptake on the follow-up scan. All scans were ^{123}I diagnostic scans and there was no intervening ^{131}I therapy. The intensity of breast uptake was semiquantitated by relating it to the intensity of thyroid (or salivary glands) uptake on the same scan.

+ = minimal uptake; ++ = moderate uptake; +++ = marked uptake; FU = full; FO = focal; CR = crescentic; IR = irregular; NE = negative.

TABLE 4
Comparison of Radioiodine Breast Uptake on Radioiodine Diagnostic and Postablation Scans

	¹²³ I diagnostic scan				
	Full	Focal	Crescentic	Irregular	Negative
¹³¹ I Postablation scan					
Full	10	2	3	2	—
Focal	1	6	—	1	7
Irregular	1	1	—	—	—
Negative	2	—	—	—	—
	¹²³ I Diagnostic scan				
	—	+	++	+++	
¹³¹ I Postablation scan					
—	—	—	2	—	—
+	3	13	—	—	—
++	4	3	2	2	—
+++	—	6	1	—	—

The scintigraphic patterns and intensity of radioiodine breast uptake were compared on the two scans in 18 patients (36 breasts). The number of breasts in each category is presented. The postablation scan was obtained within few days of, and interpreted independently from, the diagnostic scan in each patient. The intensity of breast uptake was semiquantitated by relating it to the intensity of thyroid (or salivary glands) uptake on the same scan. + = minimal uptake; ++ = moderate uptake; +++ = marked uptake.

to iodine deficiency (20,21). Whether iodine deficiency contributed to the prevalence of positive breast uptake, or whether some of our patients had dysplastic/neoplastic breast diseases, is not known. Finally, the role of elevated TSH levels or of the hypothyroid state, routinely induced before image acquisition, remains to be studied.

The presence of breast uptake, despite 4%–9% thyroid uptake of radioiodine in four patients, suggests that the breast has a relatively high affinity and/or capacity for radioiodine. The latter is supported by the observation that iodinated contrast material suppressed thyroid, but not breast, radioiodine uptake. The relatively high capacity of the breast for radioiodine uptake could be related to the larger mass of the breast or to the fact that turnover of iodine in the breast is faster, since it remains largely unorganified (22).

Radioiodine breast uptake can potentially be misinterpreted as lung metastases when:

1. A history of breastfeeding is not obtained or the occurrence of breast uptake without breastfeeding is not acknowledged.
2. The uptake is irregular or unilateral.
3. There is a coexisting lung (or other) metastasis.
4. There is a coexisting elevated thyroglobulin level but an otherwise unremarkable scan.

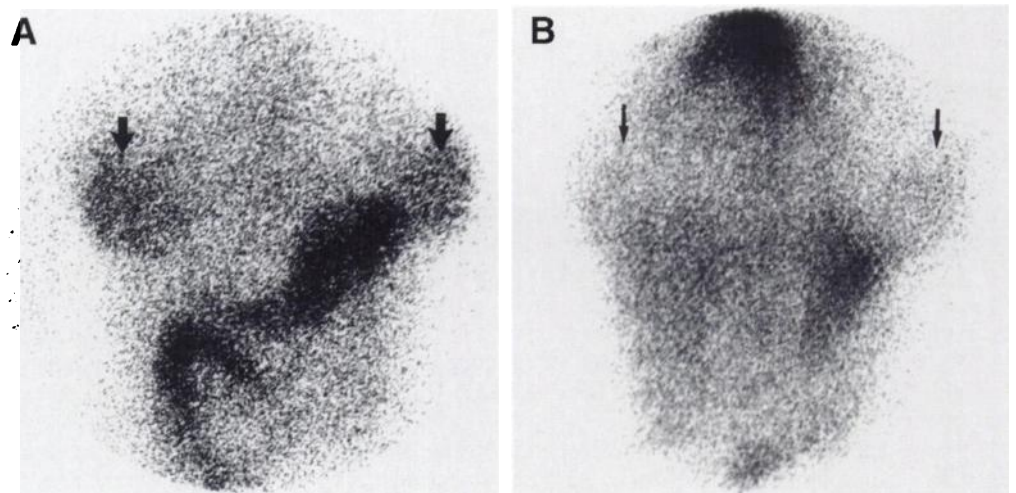


FIGURE 4. (A) Iodine-123 diagnostic scan. Anterior chest view of Patient 1. Arrows delineate ++, full breast uptake bilaterally, a picture typical of a lactating breast. (B) Iodine-131 postablation scan. Anterior view of the chest in the same patient obtained 5 days after the scan in (A). Arrows delineate minimal full breast uptake bilaterally. Breast uptake is more prominent in (A) than in (B).

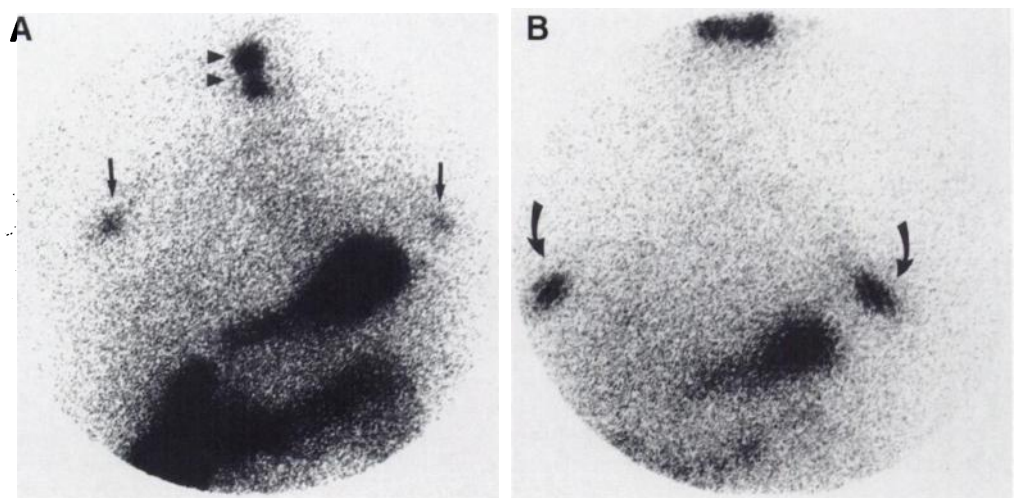


FIGURE 5. (A) Iodine-123 diagnostic scan. Anterior chest view obtained 18 mo after discontinuation of breastfeeding. Arrows delineate ++, focal and +, focal uptake, in the right and left breasts, respectively. Black triangles delineate two foci of remnant thyroid tissue. (B) Anterior chest view of a 5550-MBq ¹³¹I postablation scan obtained 5 days after the scan in (A) and after inadvertent administration of CT contrast material for an unrelated study. There is a disappearance of thyroid uptake and persistent breast (curved arrows) as well as submandibular gland uptake.

One or more of the last three conditions was present in about 50% of our patients.

Since moderately elevated prolactin levels were present only in a minority of patients with radioiodine breast uptake, the measurement of prolactin levels may not be warranted under these circumstances. A prolactin level may be best obtained a few months after resumption of thyroxine therapy if a pituitary adenoma is suspected. Finally, since a considerable fraction of the radioiodine dose may be delivered to the breast, which may be harmful (23), further studies are warranted to clarify the mechanism(s) of radioiodine breast uptake and how to prevent or reduce it.

CONCLUSION

Although the mechanism(s) for radioiodine breast uptake in the absence of breastfeeding are not clear, the uptake does not appear to be directly related to hyperprolactinemia or previous lactation or to represent blood-pool activity. Breast uptake can mimic lung metastases and should be ruled out in all female patients with radioiodine uptake in the chest area.

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