

Human Breast Uptake of Radioactive Iodine

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Increased radioiodine uptake parallels the abnormal breast tissue changes produced by iodine deficiency in rats. Pilot studies show that ^{131}I concentration in biopsied human breast tissues with carcinoma or dysplasia is higher than in histologically normal tissues from the same patient. In a two-part study employing ^{131}I and ^{125}I as the radionuclide tracers, evidence is presented showing that radioiodine uptakes in human breasts can be determined *in vivo*, that normal values by the technic employed were 10% or less, and that abnormal (ie, dysplastic or neoplastic) breast tissue has increased radioiodine uptake.

DEMOGRAPHIC evidence indicates that rates of morbidity and mortality due to breast cancer are higher in areas of iodine inadequacy than in regions where iodine is readily available.¹

When rats are fed an iodine-deficient diet, breast tissue histology is modified,² and when estrogen is also added, changes occur which are similar to those seen in human

breast dysplasia.³ Radioiodine uptake in the breast tissue of such rats is increased.¹ On histologic examination, the breast tissues in these animals show definite abnormal changes, the extent of which appears to parallel the degree of increase in radioiodine uptake.^{1,4}

Studies in rats support our hypothesis that this response to iodine lack is due to the need for iodine for maintenance of normal breast function and histologic structure.⁴ When iodine concentration in the breast is blocked by perchlorate ion, similar changes of a dysplastic nature are seen.⁵ In studies employing antithyroid drugs or athyroid animals, the same changes in breast histology do not occur.^{1,2} Background support of our hypothesis has included the findings that the breast traps iodine and organifies it,⁶ although it performs both of these activities less efficiently than the thyroid gland.

In view of the findings in rat mammary tissue, and in an effort to evaluate the radioiodine uptake levels in the human breast as indicators of histologic abnormality, a pilot study was undertaken. Patients who were to have biopsy of a breast lesion were given tracer doses (10–30 μCi of ^{131}I) the evening before surgery. Following biopsy, 100 mg of normal and 100 mg of abnormal breast tissue were obtained from the specimen and counted in a scintillation counter. In all of the 6 cases studied, the ^{131}I concentration in breast tissue with carcinoma or dysplasia was higher than that in histologically normal

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Presented in part at the Work-in-Progress at the Radiologic Society of North America, Chicago, November 1972, and Current Investigation at The American College of Obstetrics and Gynecology Meeting, Bal Harbour, May 1973.

Supported in part by the Milheim Foundation for Cancer Research and Public Health Service Grant CA AM 13186 from The National Cancer Institute.

Appreciation is expressed to Dr. Hyman Menduke for his statistical analyses.

Submitted for publication January 7, 1974.

TABLE 1. HUMAN BREAST TISSUE UPTAKE STUDIES

Patient No.	Pathologic diagnosis	Excess of counts/min/mg (abnormal minus normal)*	SD
1	Fibroadenoma	+40	±7
2	Carcinoma	+144	±5
3	Fibroadenoma	+4	±7
4	Carcinoma	+28	±8
5	Carcinoma	+46	±5
6	Fibroadenoma	+18	±7

* Differences in ¹³¹I uptake between normal and abnormal human breast tissue received at biopsy. Abnormal tissue counts were 36% higher than normal tissue counts ($P < 0.05$, Sign Test).

tissues from the same patient. The difference was significant for a P value of 0.05 (Table 1).

While these results show an overlap of uptakes when benign and malignant tissues are compared, the overall results are of a generally increased uptake in abnormal tissue, which is in keeping with data from rat studies. Radioiodine concentration in the human breast following large tracer doses has been previously reported.⁷ There have been ^{99m}Tc-pertechnetate images of human breasts with carcinoma reported, showing increased isotope concentration in neoplastic areas.^{8,9}

Considering the basic responses in rats and the human evidence, the present preliminary program was carried out to determine: *a*) whether radioiodine uptake in human breasts could be measured in vivo; *b*) if so, what the normal ranges are; and *c*) whether abnormal (ie, dysplastic or neoplastic) breasts have an increased uptake.

MATERIALS AND METHODS

The reported data consists of two parts. The earlier work with ¹³¹I was performed to determine whether breast iodine uptake could be measured and what technics could be used. For this, volunteers from only those patients having ¹³¹I uptake for diagnosis of thyroid disease were used. The second part, in which ¹²⁵I was used as the radionuclide,

included patients at high risk for breast disease as well.

Part 1

Thirty-three women, ranging in age from 20 to 61 years, who were seen in the Nuclear Medicine Laboratory over a 4-month period for radioiodine uptake studies because of suspicion of thyroid disease, volunteered to have breast uptake determinations. These women were given tracer doses of 10–30 μ Ci of ¹³¹I orally, and uptake determinations were done 24 hours later in the thyroid and in the breast.

The technic employed to determine radioiodine uptake in the breast was similar to that used for determination of thyroid uptake. The breast was supported on a mammography stand. A 1 × 1 inch sodium iodide thallium-activated crystal detector probe was centered over the breast at a distance of 20 cm. The collimator angle was 30° and gave a geometric field of view of 14 cm. Five-minute counting times were used. The tracer dose was counted in a breast phantom using the same geometry. The ¹³¹I capsule was positioned 3.5 cm below the top surface of the phantom. The majority of the breasts measured in the study had half thicknesses from 2 to 4 cm when placed on the mammography stand. For these breasts, the phantom represented an adequate geometric simulation. The occasional very large breasts were represented less well. A suitable phantom design for the very large breast will depend upon determination of the radionuclide distribution in the tissue.

Part 2

Fifty women, ranging in age from 19 to 63 years, who were seen for radioiodine uptake studies either because of suspicion of breast or thyroid disease, volunteered to have breast uptake determinations. These women were given tracer doses of 100 μ Ci of ¹²⁵I orally, and the concentration of ¹²⁵I was

determined 24 hours later in the breast and, when indicated, in the thyroid.

The method employed for ¹²³I percentage uptake determination in the breast required similar equipment to the technic described above. However, in order to avoid iodine counts from the thyroid contributing to the breast counts in this study, the thyroid was covered by a lead shield held in place by a neck orthopedic collar. The standard counting error did not exceed 2%.

In both parts of the study, a clinical breast examination was done before the breast uptake determination. A surgeon unfamiliar with the medical condition of the patient involved evaluated the breasts. All palpable masses or irregularities were recorded and biopsy was done in clinically abnormal cases. Mammography was not always included in these samples, but when possible, the patients were evaluated by x-ray technics.

RESULTS

Part 1

Uptake studies were done on a total of 65 breasts (1 patient had had a unilateral mastectomy). Of the 65 breasts, 57 were determined to be clinically normal and 8 clinically abnormal. The mean uptake value in the clinically normal breasts was 6.9%. The mean uptake value in the clinically abnormal breasts was 12.5%. These values are significantly different ($P < 0.005$) (Table 2). When the uptake values were studied as a function of the left minus the right

TABLE 2. COMPARISON OF ¹²³I UPTAKE VALUES: CLINICALLY NORMAL VERSUS CLINICALLY ABNORMAL BREASTS

	No. of breasts	Mean uptake (%) (\pm SD)	95% confidence limits
Clinically normal	57	6.9 \pm 0.46	\pm 0.9
Clinically abnormal	8	12.5 \pm 1.02	\pm 2.4

$t: 5.04; P < 0.005$

TABLE 3. STATISTICS TABLE FOR DIFFERENTIAL IN PERCENT UPTAKES OF ABNORMAL MINUS NORMAL BREAST

	$\bar{\Delta}$	Significance of Δ
Clinically normal (N)	+0.4	NS
Clinically abnormal in one breast (A)	+5.3	$P < 0.02$
$\bar{\Delta}A - \bar{\Delta}N$	+4.9	$P < 0.01$

$\bar{\Delta}$ represents the average differences in percent uptake between breasts.

$\bar{\Delta}N$ represents the difference in percent uptake between clinically normal breasts in the same patient.

$\bar{\Delta}A$ represents the difference in percent uptake between a clinically normal breast and a clinically abnormal breast in the same patient.

breast, the difference between clinically normal breasts was not significant (Table 3).

All the patients in this study were volunteers drawn from a population of women with clinical symptoms which resulted in their physicians sending them to the Nuclear Medicine Laboratory for thyroid function studies. It was of interest, therefore, to determine whether a correlation existed between the level of the thyroid uptake and breast uptake. The correlation coefficient (r^2) was 0.052, an extremely low degree of correlation. We can presume, therefore, that in this group the level of thyroid uptake did not influence the level of breast uptake.

Ten percent was determined to be the upper limit of normal for the 24-hour ¹²³I uptake by the breast. This value is 2 standard deviations below the mean of the uptake in the abnormal breasts. Uptakes equal to or greater than 10% were compared with those less than 10%. As noted in Table 4, the difference between these two groups is signif-

TABLE 4. COMPARISON OF ¹²³I BREAST UPTAKE VALUES: UPTAKES \geq 10% VERSUS UPTAKES $<$ 10%

Breast uptake	Clinically normal	Clinically abnormal	Sum
\geq 10%	9	7	16
$<$ 10%	48	1	49
TOTAL	57	8	65

$\chi^2 = 15.77; P < 0.005$

icant ($P < 0.005$). In this table, it was noted that 9 of the 57 clinically normal breasts had uptakes of $\geq 10\%$. This represents 16% of the total number of clinically normal breasts. These may be false positives or may be due to abnormalities not yet clinically apparent. However, 7 of the 8 clinically abnormal breasts (88%) had uptakes $\geq 10\%$.

Part 2

Fifty patients were employed in this portion of the study in which ¹²³I was the radio-nuclide used. As indicated previously, the patients studied included those at high risk for breast disease as well as those being studied for thyroid abnormalities. The breaking point for normal versus abnormal breast uptake levels was determined to be 9%. Uptakes equal to or greater than 9% were compared with those less than 9%. The mean uptake value of the clinically normal and abnormal breasts differed significantly ($P < 0.001$) (Table 5).

TABLE 5. ¹²³I BREAST UPTAKES (χ^2 TABLE)

	Both breasts normal up- takes (less than 9%)	One or both breasts ab- normal up- takes (9% or greater)	Totals
Both breasts normal by physical exam	31	3	34
One or both breasts abnormal by physical exam	3	13	16
TOTAL	34	16	50

Significance: $P < 0.001$

Some of these patients were also drawn from a population of women referred for thyroid function studies. Therefore, although a lead shield was used, a correlation coefficient for breast versus thyroid uptakes was calculated and was extremely low. We can presume that in this group, as in the first group, the level of thyroid uptake did not influence the level of breast uptake.

DISCUSSION

The data presented in this report confirm and extend that from previous animal studies indicating that iodine is actively metabolized in breast tissues. In addition, a relatively constant 24-hour uptake of radioiodine has been obtained in normal human breasts. By the technic employed, this does not exceed 10% and has a mean value of 3.5%

In Part 1 of this study, using ¹³¹I, a statistically significant difference in 24-hour uptake values between clinically normal and abnormal breasts was found. Clinical abnormality in the breasts of the patients who volunteered was determined by palpation and observation of the breasts by an experienced surgeon. There was seen to be an elevation of radioiodine uptake in abnormal breasts. Part 2 elaborates upon the ¹²³I study and represents our first work employing ¹²³I as the iodine tracer. This isotope with its short half-life (13.6 hours), single gamma energy, and absence of beta radiation is a much more suitable radionuclide than ¹³¹I. Again, this study shows that there is a statistically significant elevation in radioiodine uptake in clinically abnormal breasts as compared with clinically normal breasts.

In these series, 5 cases of carcinoma were found. In 2 of these, the initial indicator of abnormality was the elevated radioiodine uptake. After this finding, mammography was performed which localized the lesions for surgery. In addition, there were clinically nonmalignant abnormal findings in patients showing an elevated iodine uptake. In these patients abnormality was proven by biopsy.

The search for a simple economic dependable screening method for early detection of breast cancer continues. Thermography, roentgen mammography, and xeroradiographic breast evaluation have been shown to be useful screening methods. Interpretation of these studies requires skill and experience, and the findings in a significant number of cases studied may be equivocal.

It would be very useful, therefore, if an easily interpretable, noninvasive screening method for breast abnormality could be made generally available. While it is not of consequence to find a laboratory test, even a noninvasive laboratory test, which only equals the accuracy of clinical examination, there is evidence that prepalpable lesions may be determined by this technic.

Other technics using radionuclides for detection of breast cancer have been reported. A recently published study describes ^{99m}Tc (technetium) images of the breast in 6 patients.⁹ The localization of the radionuclide in breast masses correlated well with clinical examination, mammography, and when available, with malignant pathologic diagnosis. Since ^{99m}Tc is handled similarly to iodine in the trapping mechanism, these findings support our observations.

As a diagnostic technic this method requires further verification by means other than clinical examination, eg, thermography, mammography, xeroradiography, and histologic confirmation. The technic could have a number of advantages, including: *a*) simplicity of method of determination; *b*) economy and general availability of necessary equipment and personnel; *c*) ease of interpretation; and *d*) provision of early evidence of breast tissue changes. In part, these would satisfy the criteria outlined by the National Cancer Program to extend and improve procedures for screening of population groups.¹⁰

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Accepted for publication February 25, 1974.