Breast Cancer Missed by Mammography

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Because a "negative" mammogram that is followed by a biopsy diagnostic of cancer is a matter of deep concern, a retrospective review was conducted of 48 such missed diagnoses at four Breast Cancer Detection Centers. The study group comprised 40,000 women participating in breast cancer screening examinations. From 3,271 biopsies during screening, 499 cancers had been found. Biopsies in the interval between screening examinations totaled 630 and yielded 48 malignancies. These 48 interval cancers were studied in an attempt to discover why they were not found on the preceding mammographic examination.

Three major categories of error were disclosed and each is discussed: (1) poor radiographic technique; (2) absence of radiographic criteria of cancer; (3a) obvious oversight by the radiologist; and (3b) lack of recognition of subtle radiographic signs. This last reason is discussed in detail in the belief that better recognition of these indirect radiographic signs will lead to more accurate diagnoses, particularly in early cancers.

The combination of mammography and physical examination has proved to be effective in detecting stage I breast cancers. Even with these diagnostic methods, however, some cancers are being missed. The dedicated mammographer has long been plagued by the "negative" mammogram which is followed by a surgical biopsy positive for breast cancer. We believe that a retrospective analysis of the objective data (i.e., serial mammograms) of patients with negative mammograms who were subsequently found to have interval cancers might be helpful in determining why these cancers had been overlooked originally.

In such an analysis, one must keep in mind that many in situ and intraductal lesions demonstrate no obvious radiographic patterns. Although the surgeon often assumes that what he palpated was the lesion found at biopsy, this is often not the case. The so-called "minimal" breast lesions are usually too small to be palpated and are more often found incidental to the biopsy of a benign process. On the other hand, there *are* subtle radiographic signs, not always recognized, that can lead to more accurate diagnosis of these earliest cancers, and these signs will be discussed.

For the purpose of this discussion, minimal breast cancer is defined as in the National Cancer Institute guidelines: a lesion no more than 1 cm in diameter. The more generally accepted definition of the term is that originally offered by Gallager and Martin in 1971 [1, 2]: a noninvasive intraductal carcinoma, a lobular carcinoma in situ, or an invasive carcinoma forming a mass with a volume no greater than a sphere 0.5 cm in diameter.

At this juncture, the question arises of whether the detection of minimal breast cancers by mammography is any less serendipitous than by physical examination. If so, one would expect a higher percentage of minimal cancers to be found in a screened population during the incidence years than in the prevalence years of the screening program. Statistics from two Breast Cancer Detection Centers (at Cincinnati and Milwaukee) revealed this to be the case. In the initial examinations of about 20,000 women (prevalence rate), 31% of the cancers found by physical examination were minimal lesions, compared with 38% of those found by mammography. However, in subsequent examinations of the same women (incidence rate), only 17% of the cancers found by physical examination were minimal, in contrast to 55% of those found by mammography. Thus it seems that finding minimal breast cancers by physical examination is largely serendipitous, but finding them by mammographic examination is not.

More puzzling, though, is the problem of a "negative" mammogram in a patient who has a true invasive lesion. One reason for missed diagnoses is poor mammographic technique. The importance of careful positioning cannot be overemphasized. It is difficult to image a lesion that is high on the chest wall or in the tail of the breast. Some masses are mobile and, in positioning the patient, the technician may allow the mass to slip out of the imaging field.

Even if the possibility of poor imaging technique is excluded, a disturbing number of clinically palpable lesions overlooked by the mammographer are noted. To determine the extent of the problem and the reasons for the missed diagnoses in these cases, we reviewed the statistics from four Breast Cancer Detection Centers (Houston, Cincinnati, Milwaukee, and Seattle).

Subjects and Methods

The study group consisted of slightly more than 40,000 women who had participated in the Breast Cancer Detection Program for 3–5 years. In this group, 3,271 biopsies had been performed as a result of the screening examinations and 499 cancers had been found (15.25%). This percentage of positive biopsies is less than the generally accepted figure of 25% in nonscreened hospital studies. It is not likely that the accuracy of biopsies in the screening program is less accurate than that of the community as a whole, leading to the question of whether an excess number of biopsies are being performed as a result of the screening examination. Another possibility would be that the screening program, in finding more *early* cancers than are generally biopsied in the community, requires a concomitant increase in the number of doubtful and negative biopsies.

Received July 25, 1978; accepted after revision January 15, 1979.

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Interval cancers are those whose signs or symptoms were first detected by the woman or her personal physician subsequent to a screening examination in which she had both a negative mammogram and a negative physical examination. There were 630 such biopsies performed and 48 cancers found (7.6%). It is important to note that the discovery rate of the screening program biopsies (15.25%) was twice that of the interval biopsies (7.6%). It is also rewarding to realize that 91.2% of the total cancers diagnosed were found as a direct result of the screening examinations.

Of the 48 cases in which cancer might have been overlooked in the preceding mammographic examination, some could have grown so rapidly as not to be present at the last examination; the intervals between screening and discovery of the interval cancers ranged from 1 to 23 months. However, 11 of these cancers were found within 6 months of the last screening examination, and all were found on retrospective review of the mammograms. Most of the remaining cancers were probably present, but were either not detected or were not detectable by current techniques.

All 48 patients with interval cancers were symptomatic at the time of diagnosis. Two had crusting of the nipple, two had bleeding from the nipple, one had pain in the breast, and 43 had palpable masses. Of the 43 palpated masses, 10 were found at surgery to be cysts, and the cancers were found incidentally; five were lobular in situ carcinoma and five intraductal carcinoma. These figures perhaps lend support to the hypothesis of Gallager and Martin [3] that some breast cancers cause excitation of surrounding tissues and an increase of periductal collagen or background stromal collagen, or even excitation of fibrocystic disease. This finding, although not yet fully confirmed, may have value in mammographic diagnosis of early breast cancers.

It is of considerable importance that 21% of these interval cancers (10 of 48) were classified as *minimal* cancers. This emphasizes the need for biopsy in any case involving thickening of breast tissue, nipple change, or nipple discharge. Detection of minimal cancers obviously cannot approach the accuracy rate of the larger, more invasive lesions, but progress can be made with more attention to the earliest signs.

The age distribution of the 48 patients with interval cancers is of some interest. Exactly half were 50 years old or younger. Five were 30–40 years old; 19 were 41–50; 17 were 51–60; and seven were 61–70. The right breast was the site of the lesion in 21 cases and the left breast in 27 cases.

Despite the fact that surgery was performed after symptoms and clinical signs were present, only 19 of these patients had positive axillary nodes. Roughly half the women in this study reported regular self-examination of their breast and virtually all reported some self-examination. Thus one would expect their cancers to be detected at an earlier stage than those found in a nonscreened population.

The 48 interval cancers were classified according to Wolfe's parenchymal patterns [4] (table 1). On pathologic examination, 41 of the lesions were invasive ductal carcinoma, three were medullary carcinoma, two were lobular invasive carcinoma, one was anaplastic carcinoma, and one was undifferentiated sarcoma. The anaplastic carcinoma and the sarcoma could fit the hypothesized category of rapidly growing neoplasm that does not show a diagnostic radiographic pattern. Medullary carcinomas are usually seen radiographically as a circumscribed mass which, especially in younger patients, may be misinterpreted as a cyst. Invasive ductal cancers are usually thought to have diagnostic patterns on mammography, and scrutiny of this group should yield important information about missed diagnoses.

TABLE 1

Cancers Missed on Mammography, Grouped by Wolfe's Classification [4]

	No.	%
N1	1	2.08
P1	11	22.92
P2	27	56.25
DY	9	18.75
Total	48	100

Results and Discussion

On the assumption that most of these 48 interval cancers had been present, although undetected, on the preceding screening examination, we reviewed the mammograms in each case. A blind reading of these mammograms mixed with a random day's screening would more accurately determine the true detectability of these lesions. However, we were more interested in determining *why* the interval cancers were overlooked, and for this reason the readings were done with prior knowledge of the diagnosis in each case.

In this retrospective examination, 14 cases (29%) were obvious oversights on the part of the original examiner (table 2); the cancers were readily apparent to the reviewer. Sixteen cases (33%) were still found to be lacking any radiographic evidence of cancer, despite the reviewer's knowledge of the diagnosis and site of the lesion.

The most interesting group was the 18 cases (38%) that were found on review to have subtle and indirect radiographic signs pointing to the diagnosis. Of these cases, 13 demonstrated asymmetry of breast tissue, with this being the only radiographic sign suggestive of a neoplastic process [5]. Two cases displayed the developing density sign [2, 5]; when compared with previous records, the mammograms displayed a progressive increase in density in a specific area without other signs. The other three cases displayed groups of calcifications that had been observed originally, but misinterpreted as benign. Later these calcifications were found to be associated with the malignant lesions [6].

In radiographic interpretation of mammograms, there are two major categories of diagnostic criteria: (1) direct signs: those provided by the cancer itself, which may be divided into primary signs and secondary signs, and (2) indirect signs: those not provided by the cancer itself but, rather, related to tissue reaction in the region of the cancer. Indirect signs may be shared by many benign proliferative disorders, but may also be vital to an early diagnosis of cancer.

Of the direct signs, the most important primary one is the presence of a mass, the characteristics of which have been thoroughly described. The direct signs that are secondary to the presence of a lesion are skin thickening, nipple retraction, diffuse lymphedema, spiculation, architectural deformity, and ulceration. These direct signs are rarely overlooked and require no elaboration here.

TABLE 2

Analysis of Mammography Errors

	No.	%
Inevitable error: no diagnostic radiographic signs found on review	16	33
Obvious oversight: diagnostic signs immediately apparent on review	14	29
Less obvious error: subtle radiographic signs noted by experienced examiner	18	38
Total	48	100

The indirect signs are more subtle and therefore go unrecognized more often. Five of these indirect signs are particularly important:

1. A solitary dilated duct under the areola or an unusual complex of dilated ducts that extends 3 cm or more within the breast. Either should invariably be considered suspicious of malignancy [3].

2. Intraductal and intralobular calcifications. Martin [6] reported that calcifications most likely to be associated with malignancy are those that are thin linear, thin curvilinear, or thin branching in pattern. Benign groupings usually appear as clusters of punctate calcifications. Whether or not the calcifications are characteristic of malignancy, it is better to biopsy, as any of these can be a subtle indication of an in situ or minimally invasive lesion.

3. A progressive density in a specific area is an important indicator which requires baseline mammograms for comparison. The breast is primarily an involuting organ, and when the mammogram demonstrates new or progressively increasing areas of density which were not present on previous studies, carcinoma should be suspected [2, 5].

4. Asymmetry of breast tissue. Any asymmetry noted in comparing two projections of the right and left breasts is an important sign [5], even with fibrocystic disease. This particular observation is overlooked more often than any other simple diagnostic criterion because many observers fail to compare the breasts. If the asymmetry is associated with any clinically palpable lesion, whether this is a mass or only an area of thickening, the yield for carcinoma is sufficiently high to warrant a recommendation for biopsy. In cases of asymmetry unaccompanied by other clinical signs, a multifocal intraductal carcinoma may be found, although the radiographic density is produced simply by the stimulation of secondary collagenosis in the breast [3].

5. A benign-appearing mass in a peri- or postmenopausal woman may be a valuable sign, as fibroadenomas can be associated with minimal lesions within or adjacent to the fibroadenoma. Thus while fibroadenomas in themselves are not considered preneoplastic lesions, they arise in the same background stroma of proliferative disorders, and it is probably wise to consider surgical excision of a solitary, dominant, noncalcified, benign-appearing fibroadenoma. In addition, a well circumscribed carcinoma may on occasion be misdiagnosed as a fibroadenoma.

ACKNOWLEDGMENT

We thank Dr. Thomas Carlile, Director, Breast Cancer Detection Center, Seattle, Washington for assistance.

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