

Tumors of the Breast Occurring in Hawaii *

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IT HAS BEEN observed over the past many years that in Hawaii race susceptibility to many diseases varies considerably. This has been particularly true as regards diseases of the thyroid, the prostate, skin and stomach.^{18, 19, 20, 22} While it has been our belief locally that tumors of the breast also fall into this category, so far as I have been able to determine, no one has made a study of significant statistics to determine this point.

At the Straub Clinic, the records of 1,080 tumors of the breast which have been surgically removed and examined microscopically are available for study. Some of the records of the tumors removed in early years are not complete, particularly as regards their morphology, and therefore have not been included.

As a working basis, we have found that most tumors of the breast fall into one of the following broad categories: (1) fibrocystic disease; (2) fibromas; (3) papillomas; and (4) malignancy. The term fibrocystic disease in this discussion will include that group of lesions of the breast which probably have a common etiological factor but which various pathologists describe under a great variety of names depending largely on the predominance of fibrous or epithelial hyperplasia, the formation of cysts and other factors quite beyond my powers of comprehension. Since the tumors we have removed have been examined by a number of different pathologists trained in various medical centers, the terminologies used have been correspondingly varied.

To indicate the confusion that exists regarding this poorly understood abnormality, the following diagnostic terms have been

used which I believe are more or less synonymous with fibrocystic disease.

- (1) Blue dome cyst (Bloodgood)
- (2) Schimmelbusch's disease
- (3) Mazoplasia
- (4) Adenosis
- (5) Fibrous hyperplasia
- (6) Adenofibrosis
- (7) Hyperplasia of breast tissue
- (8) Fibrous and glandular hypertrophy
- (9) Non-uniform breast hypertrophy
- (10) Sclerosing mastitis
- (11) Mastopathy
- (12) Nodular hyperplasia
- (13) Cyclomastopathy
- (14) Chronic mastitis
- (15) Mammary dysplasia
- (16) Mastodynia
- (17) Adenocystic disease
- (18) Cystiphorous—desquamative epithelial hyperplasia
- (19) Epithelial hyperplasia
- (20) Intraductal papillomatosis
- (21) Apocrine hyperplasia
- (22) Cystic glandular hyperplasia

Dr. Irvin Tilden, pathologist of the Straub Clinic, after reading the above made the following comments:

In *mazoplasia*, *adenofibrosis*, *fibrosis*, *periductal fibrosis*, there is no cyst formation, though there may be slight cystic dilatation of ducts, the condition is more physiological than pathological, there is pain with menstrual periods, and fine nodularity to palpation.

In *fibrocystic disease*, *cystic mastopathy*, *Schimmelbusch's disease*, *chronic cystic mastitis*, *cystiphorous desquamative epithelial hyperplasia*, and others, these terms are synonymous and embrace many more

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specific morphologic states which may occur singly or in various combinations:

1. *Fibrosis* of varying amount and kind.
2. *Cyst formation, cystic dilatation of ducts, blue dome cyst*, depending upon number and size of cysts.
3. *Apocrine hyperplasia or metaplasia*. (The epithelium lining ducts or cysts becomes acidophilic and morphologically identical with epithelium of apocrine sweat glands.)
4. *Blunt duct adenosis*.
5. *Sclerosing adenosis or sclerosing fibroadenomatosis*. (Clinically and pathologically this state may be confused with cancer.)
6. *Intraductal epithelial hyperplasia, intraductal papillomatosis, precancerous hyperplasia*. (This last phase is the one which is definitely related to cancer.)

From the point of view of the surgeon, at least, the only practical considerations are: is the tumor now malignant or does it represent a condition that is likely to become malignant in the future?

An analysis of the 1,080 removed tumors showed that 220 were malignant, 476 were fibrocystic disease, 256 were fibroadenomas and 20 were ductal papillomas. The remainder of the tumors consisted of various odds and ends such as lipomas, plasma cell mastitis, fat necrosis, adenoma, cystosarcoma phylloides, gynecomastia, etc. Of the 220 malignancies, 32 occurred in Japanese women and one in a non-Japanese male. The population of the Territory is approximately 40 per cent Japanese and the percentage of Japanese seeking medical care at our clinic probably approximates this ratio; hence, it is evident that carcinoma of the breast in Japanese women is relatively rare, being I believe about four times more common in races other than Japanese. A popular belief is that it may be due to Japanese mothers nursing their children for a greater length of time than other races do. Since the second generation of Japanese

almost universally adopt Western ways of living, it will be interesting to see if carcinoma of the breast becomes more prevalent in future years.

The importance of removing all tumors or areas in the breast that are abnormal, without delay, when there is a question of their nature—and there is always this question—is appreciated by most physicians, but its importance still needs emphasis because there are some individuals who are supposed to speak with authority who believe there is room for procrastination under certain circumstances. My observations over the years have convinced me, after some unfortunate experiences, that if the patient is physically fit to withstand operation, no tumor should ever be watched regardless of the patient's previous history. The tendency to procrastinate is particularly evident when on previous occasions tumors have been removed and they were found to represent some form of mastitis, cystic mastitis in particular. In all probability the tumor will again prove to be benign, but of this no one can be sure for I have on several occasions, under such circumstances, removed a tumor showing an area of malignancy. The following two case reports illustrate this point.

Case 1. A Caucasian woman, age 45, had a tumor removed from the left breast in June, 1938. The microscopic diagnosis was mazoplasia. Another tumor was removed from the same breast in May, 1939, and again in July, 1939; microscopic diagnosis at this time was benign cystic disease. In June, 1940, the right breast was explored. There were many cysts present. A nodule in the lower quadrant of the breast was reported to be benign. Another nodule in the upper outer quadrant was found to contain a Grade III adenocarcinoma. Radical mastectomy was done and two months later a simple mastectomy was done on the other side. There was no evidence of axillary metastases and the patient has remained well to date.

Case 2. A 42-year-old Caucasian woman was first seen on August 7, 1944, with a history that 8 to 10 years previously, she had had two cysts removed from the left breast. On examination a tumor was palpable in the upper quadrant of the

right breast. This tumor was removed and reported to show a simple cyst of the breast. The patient subsequently had another similar lesion removed from the left breast elsewhere. She was next seen by me on October 15, 1955. There was a small tumor just behind the nipple on the left that had been noticed for 2 weeks. It was my belief that this in all probability again represented some type of mastitis. However, she was informed that no one could be sure of this, and she was advised to have the tumor removed. This was done on October 18, 1955, and much to our surprise, this proved to be an adenocarcinoma, Grade II, without axillary metastases.

Not infrequently on examining a breast in an individual who suspects something is wrong, usually because of pain, or on routine examination, an area is found which is questionably abnormal. Under these circumstances, it is reassuring to have the opinion of another physician whose judgment one values. If one is still uncertain as to the possibility of an existing abnormality, it is advisable for the patient to return at short intervals for re-examination until a definite opinion is reached. Many patients are alarmed because of painful tender breasts, but if no localized abnormality is detected—and this is frequently the case—the patient only needs reassurance.

To advise a woman that she has a tumor of the breast, the nature of which cannot be determined with assurance without microscopic examination, creates a situation that is very distressing to most patients, and it is a situation that some physicians, particularly in their younger years, hesitate to bring about. It is a responsibility, however, which no one should be unwilling to assume. Another situation even more distressing to all concerned is to assure the patient and family after removing a breast tumor that all is serene and in a few days be informed by the pathologist, after more careful study, that a small area of malignancy has been found.

One is rarely justified in proceeding with a radical mastectomy without biopsy confirmation that the lesion is malignant. It is

always desirable to remove the primary tumor in its entirety because it gives the pathologist an opportunity to select for examination the areas most suspicious, if the malignancy is not widespread, and it helps prevent, no doubt, local dissemination of tumor cells. The danger of missing a small area of malignancy in a tumor of the breast by resorting to needle biopsy, regardless of one's clinical impression as to what the nature of the tumor may be, is too great, in my opinion, to ever justify the use of this instrument.

How best to handle patients with recurring tumors of the breast due to some form of mastitis is a problem no one has solved with any degree of satisfaction. After one has on numerous occasions removed tumors first in one breast, then the other, and finally one is removed in which an area of malignancy is found, suspicion should be created in everyone's mind that some forms of mastitis, at least, have potential possibilities as a forerunner of malignancy. I believe it is most pathologists' experience that many carcinomas of the breast are associated with some type of mastitis.

How many times is one justified in removing tumors from the breasts showing some form of mastitis before advising bilateral simple mastectomy? Perhaps the pathologist can foretell some types of mastitis that are thought to predispose to malignancy by the hyperactivity of the cellular elements. Of this, I have not been too much impressed. The solution of the problem is usually automatically taken care of because the patient almost universally refuses to entertain the idea of bilateral mastectomy. Were it not for the psychologic trauma involved, women with such an affliction would be better off bosomless. It reminds me of a remark I heard Dr. Charles Mayo make many years ago while watching him remove a uterus with carcinoma. He said it was too bad when women reach the menopause that their wombs did not drop out instead of their teeth. Be that as it may, it

is never safe to conclude that any lump in a woman's breast is not malignant because previous ones have been benign.

In our statistics, exclusive of Japanese, it was found that fibrocystic disease occurred 2.3 times more frequently than fibroadenoma. In Japanese, there were 88 fibroadenomas and 80 cases of fibrocystic disease. Fibrocystic disease occurred about three times more frequently in non-Japanese races. One wonders if the relative infrequency of fibrocystic disease in Japanese women does not have a direct relationship to the relative infrequency of carcinoma.

The most commonly found tumors occurring in young women are fibroadenomas, and it is, in our experience, the most common tumor found in Japanese of all ages. These are solid, firm, round, frequently lobulated, freely movable tumors consisting principally of connective tissue with varying degrees of hypertrophy of glandular and ductal epithelium. These tumors are usually single, though occasionally multiple. Once they are removed, they are not prone to recur. In one individual, a Japanese, fibroadenomas continued to recur with such frequency that a simple mastectomy was done. While fibroadenomas are usually easy to diagnose clinically because of the age group in which they occur and their physical characteristics, such tumors should always be removed and subjected to histologic examination because no one can ever be sure of their benignancy. I have been guilty of removing a small circumscribed freely movable tumor in my office which I thought without question to be a fibroadenoma and found, to my surprise, that it was a carcinoma.

Chronic cystic mastitis occurs more frequently in women of middle life and is often associated with premenstrual breast pain. The breasts are frequently tender and have a shotty grape-like feel on palpation. As long as the breast feels uniform in consistency, no one need be alarmed, but once an area develops that is abnormal, as com-

pared to the remainder of the breast, this area should be biopsied.

Discharge from the Nipple. Nipple discharge regardless of its color or composition when the individual is not lactating, presents a problem about which there is much difference of opinion. Much has been written about this condition, and it is surprising what a variety of conclusions have been reached by competent observers with wide experience. For instance, Bloodgood² stated, "Discharge from the nipple, like pain, is not an indication of a lesion of the breast for which operation is indicated. There is no evidence that these lesions are precancerous and the prevailing view that a woman with a discharge from the nipple should be protected from cancer by the removal of the breast is based on fear, not fact." Lewison and Chambers,⁶ reporting from the same clinic some 30 years later, found in 2,195 patients with variegated breast disease that 114, or 5.2 per cent, had a discharge from the nipple. Benign breast diseases, which included chronic cystic disease, fibroadenoma and papilloma, accounted for the discharge in 80 per cent, whereas malignant breast disease, including Paget's disease, was responsible in 20 per cent of the cases. They further state that the evidence indicates that no one type of nipple discharge is specific for a particular type of breast lesion, and consequently cancer, as well as benign breast disease, can give rise to diverse types of nipple discharge. However, in all cases of papilloma, there was either a serous or a serosanguinous secretion from the nipple. Gray and Wood⁵ emphasized that discharge from the nipple of any nature whatsoever is of great significance. Donnelly,³ reporting on 219 patients with nipple discharge which represented 9.2 per cent of cases of breast lesions, found that 37, or 17 per cent, did not have a palpable mass when examined. All but one of these patients were operated upon. Thirty of the lesions showed definite evidence of hyperplasia. Five patients had a malignant lesion

and six patients had lesions showing definite precancerous tendencies. Kilgore¹⁰ and co-workers, reporting on 190 patients with nipple discharge, found that if secretory elements consisting of fat droplets and desquamated cells were present microscopically, the discharge appeared to be of little significance. A serous discharge without secretory elements will in many cases sooner or later be found to contain blood. In the presence of a bloody discharge, without palpable lump, cancer was found to be present in one in 20 to 25 cases. If cancer is not present, the bleeding is probably coming from papillary disease. As they point out, if a patient with nipple discharge has a palpable mass, the discharge becomes of secondary importance since the mass should always be removed for examination. Haagensen, Stout and Phillips,⁶ studying 353 cases of intraductal papillary cystic adenomas, found that the overwhelming majority of these intraductal papillomas are situated in the central area of the breast and the larger ducts near the termination in the nipple. Also that since the vast majority of bloody discharge from the nipple is due to benign papilloma, and rarely to papillary carcinoma, the pathologist should be very careful in diagnosing carcinoma. When the pathologist is in doubt as to the nature of the lesion, more extensive surgical procedure should be delayed in order to permit more careful study of permanent sections. Even though the lesions prove to be malignant, they are relatively benign, and reasonable delay will not impair the chances of cure by later radical surgery.

Apparently it has been most observers' experience that cytologic study of nipple discharge is not sufficiently reliable to base therapy upon. Fleming⁴ who apparently has had a considerable experience in examining discharges from the nipple recently stated, "Color and/or character of nipple discharge aside from a bloody discharge seems to have little significance from a practical management standpoint. It is to

be emphasized that while this newer method of study is of considerable value in the management of certain lesions of the breast, it does not eliminate the necessity of histological confirmation of any positive smears. Conversely, a negative cytology study has no value in establishing the benign nature of a lesion of the breast." If these statements are correct—and I believe they are—why bother to examine discharges from the nipple at all?

Dr. Tilden, who has taken an active part in the cytological laboratory of the local Cancer Society since its inception, was kind enough to furnish me with the data which they have accumulated. Since July 25, 1949, to January 1, 1956, 150 patients with nipple discharge have been examined. Four were reported to show carcinoma cells and all four were verified to have cancer by operation. Two were reported suspicious and three atypical, benign. No adequate follow up has been reported in these cases.

In reviewing the histories and physical examinations of the four positive cases, it is evident that they had lesions that by all means should have been biopsied. Until and unless data is accumulated to show that examination of nipple discharge is of more practical value than it would seem to be to date, I see little reason to place any reliance on this method of examination.

Carcinoma of the Breast. In the treatment for carcinoma of the breast, we usually adhere to the principles laid down by Meyer and Halsted and have refrained except very exceptionally from extending the operation supraclavicularly or to include the internal mammary node chain or other mediastinal structures, as recommended by Wangenstein, Urban and others. Wangenstein²⁴ has stated that the Halsted operation for carcinoma of the breast is incomplete and outmoded. In selected cases, he advocates a wide removal of cervical, axillary, mediastinal and internal mammary lymph node chain.

It has long been known that the internal

mammary lymph node chain may be the seat of metastases, particularly when the inner quadrants of the breast are the areas involved. In 1928, I saw Sir Sampson Handley at Middlesex Hospital, in London, inserting radium intracostally in the treatment of breast cancer. His son, R. S. Handley,⁸ is carrying on with this work and in 139 cases of breast cancer considered to be operable, he found 29 per cent with metastases to the internal mammary chain. This involvement occurred three times more frequently when the inner quadrants of the breast were the site of the primary lesion. Urban²³ in his recent paper before the Pan-Pacific Surgical Association meeting reported on 150 radical mastectomies for carcinoma of the breast with en bloc in continuity resection of the internal mammary lymph node chain with one death. In 13 per cent of the cases where the axilla was clear, there were metastases to the internal mammary lymph nodes. To me this seems to be a logical procedure when the primary lesion is situated in the inner quadrants of the breast. These newer innovations are being watched with interest, but until their superiority is conclusively demonstrated over the more conservative type of operation, we feel that we are not justified in adopting them routinely.

In analyzing the data regarding the 32 cases of cancer of the breast in Japanese women, it was found from the history that the average duration had been one year. In other races, the average duration had been four months. Metastasis to axillary nodes in Japanese was 56 per cent and in other races approximately 48 per cent. This series of cases is entirely too small to permit drawing of conclusions, but it does indicate that Japanese women particularly the older age group have not been indoctrinated as to the possible seriousness of tumors in the breast. It might further suggest that the longer the duration of the primary lesion, the more likely the possibility of axillary metastasis. The significance of

axillary metastasis assumes great importance when it is realized that the five-year survival of patients with axillary metastasis is around 30 to 40 per cent as compared to 65 to 85 per cent without such nodal involvement.⁹

There has been much discussion of the McWhirten¹⁵ method of handling breast cancer by simple mastectomy and intensive postoperative irradiation of the areas to which metastasis usually occurs. With this procedure, we have had no experience. Judging from the literature, results have not been as good as when the accepted method of radical surgical removal has been used and complications following such intensive irradiation have been considerable and are becoming more apparent with the lapse of time.

Ackerman¹ concluded after a careful study of McWhirten's cases, "It is our belief at the conclusion of this study that if patients are properly selected for radical mastectomy and operated upon by the trained surgeon, this method of treatment must yield in this group, the greatest number of permanently cured patients."

The role that postoperative irradiation should play in the treatment of breast malignancy is hard to evaluate. We follow the practice advised by many of treating cases that are demonstrated to have axillary metastasis. Everyone recognizes the difficulty of being sure that such spread has not occurred. The more carefully the pathologist examines the axillary nodes, the higher the incidence of involvement. Serial sections of all lymph nodes is impractical and yet when this is done, the incidence of involvement has been found to increase considerably. Most everyone recommends irradiation when recurrence takes place. It would seem that a few malignant cells either already present or disseminated at the time of operation would be more susceptible to irradiation at an early date rather than later after they have become more firmly entrenched. With these possibilities in mind,

it would seem logical to recommend irradiation routinely.

The value of removing gonads and adrenal glands or the hypophysis in the treatment of breast cancer is based on the fact that when the tissue in which malignancy develops is functionally dependent upon hormonal (estrogen) activity, this property may be transmitted to neoplasms arising in such tissue. Our experience with 10 cases²¹ in whom we have done oophorectomy and bilateral adrenalectomy has not left us with much enthusiasm for this approach to the treatment of recurrent mammary malignancy though several cases underwent remarkable though temporary improvement.

It has been shown experimentally and otherwise that hypophysectomy produces a marked decrease in the production and excretion of 17-ketosteroids and this is a sign of adrenal-cortical and gonadal insufficiency. Thus by one operation, it is hoped to eliminate the production of steroid hormones that arise from this action. Little if anything is apparently known about the hypophysis and its relation, if any, to carcinogenesis.

In a recent article by Luft and Olivecrona¹³ the results of 37 hypophysectomies were reported. While this is too small a series from which to draw conclusions, it seemed to me that results closely paralleled those obtained by bilateral oophorectomy and adrenalectomy. Perhaps further experiences with hypophysectomy may provide more encouragement but of this I am skeptical.

The use of androgen (testosterone) in the treatment of breast malignancy has been advocated for approximately 15 years. Our experience in common with others has been that some cases show marked but temporary improvement. Pearson¹⁷ and associates from the Memorial Hospital in New York recently reviewed their experiences with hormonal therapy for breast cancer. They found that approximately 23 per cent of women with breast cancer ob-

tained objective improvement which on the average lasted 7.5 months. While the action of androgen is unknown, it is thought to neutralize the effects of estrogen. They have never obtained a definite remission with the use of androgen in a patient with a non-estrogen dependent lesion. Since they estimate that approximately 50 per cent of women have an estrogen dependent type of malignancy, it is evident that androgen is not a very effective neutralizing agent if that is its method of action.

It has been observed that androgen may at times accentuate the growth of mammary cancer and some evidence has been accumulated to show that in these cases androgen is converted into estrogen. Paradoxical as it may seem, it has been found⁷ that some patients are benefited by estrogen administration. This has been found to occur in the older postmenopausal patients. Its use is a potential hazard since it has been found that approximately 50 per cent of women of all ages appear to have estrogen dependent type of cancer. It has been suggested that the beneficial effects of estrogen are due to suppressing pituitary function. It has been demonstrated that cortisone in doses of 200 to 300 mg. per day has induced objective remission in patients with non-estrogen dependent cancer. Unfortunately, there is no way of telling beforehand which patients will respond to these methods of therapy. At best, they afford only temporary respite from the inevitable progress of the disease.

The belief that early detection of breast cancer and early accepted methods of treatment has contributed little to the ultimate cure or length of survival of patients is a theme one sees not infrequently discussed in current medical literature, lay periodicals and even in the press. MacDonald¹⁴ presents evidence to show, as he expresses it, that the wide range of biological potential, exhibited by human cancer, is determined early in the preclinical phase of the disease and probably in the actual induction phase

of mazoplasia, and that undue emphasis on early treatment ignores the complex biological nature of cancer.

Park and Lees,¹⁶ after extensive study of current literature, concluded that it has not been proved that the survival rate of cancer of the breast is affected by treatment at all, that the evidence strongly suggests that treatment is quite ineffectual in reducing the incidence of death from metastatic spread and that if treatment is in any way effective, the effectiveness cannot be greater than that required to increase the overall five-year survival rate by more than 5 to 10 per cent.

Kraus,¹¹ reviewing the same literature and statistics that were studied by Park and Lees, concluded that "Early treatment is effective to a very considerable extent in breast cancer and that the literature fails to provide any evidence to detract from this conclusion."

It seems to be the old story of making statistics prove most anything. If twisted sufficiently, they probably occasionally tell the truth.

The belief that early surgical intervention is of little importance in the treatment of cancer is contrary to our fundamental teaching of the past. Everyone has had the experience of operating on a small supposedly early cancer of the breast to find widespread axillary metastases, and on the other hand of removing a lump in the breast of known long duration which proved to be cancer without any detectable axillary metastases. In neither case can one be sure how long the primary malignancy has been present. The history is not dependable because some women present themselves with a large tumor which they say they have just recognized but which obviously has been present for many months. Some tumors arise in large pendulous breasts and are not easy of recognition. There is a great variation in frequency of self examination of breasts and intelligence in interpretation of these findings. No doubt some primary

lesions metastasize much earlier than others due to either inherent properties within the tumor, to lack of tissue resistance on the part of the host, or perhaps to accidental early invasion of lymphatics or the blood stream. Certainly at some moment, the tumor in the breast must be localized, at some unknown time it may have spread, but is still amenable to complete extirpation resulting in cure of the patient and at some unknown later moment, the cells have spread beyond the scope of resectability and surgery cannot produce a cure. If this is the train of events that takes place, is it not logical to subject all individuals with such lesions to emergency operation?

To publicize the belief without conclusive proof in medical journals and in periodicals widely read by the lay public that early detection and early operation for cancer is of doubtful value will destroy the fruits of the tremendous efforts that have been made in recent years in encouraging the public to consult their physicians when any tumor is noticed. It would seem that such publicity should be curtailed until, or unless, more definite proof of its correctness has been established.

In concluding these remarks, it would seem appropriate to emphasize:

1. Cancer of the breast in Japanese women is rare and fibrocystic disease is correspondingly rare. The frequency of fibrocystic disease and breast cancer in Japanese has about the same relationship as it has in other races. For this reason, perhaps one might be influenced to believe that fibrocystic disease is a precursor of breast malignancy.

2. All tumors of the breast without exception should be removed without delay and subjected to microscopic examination.

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