TUMORS of the BREAST

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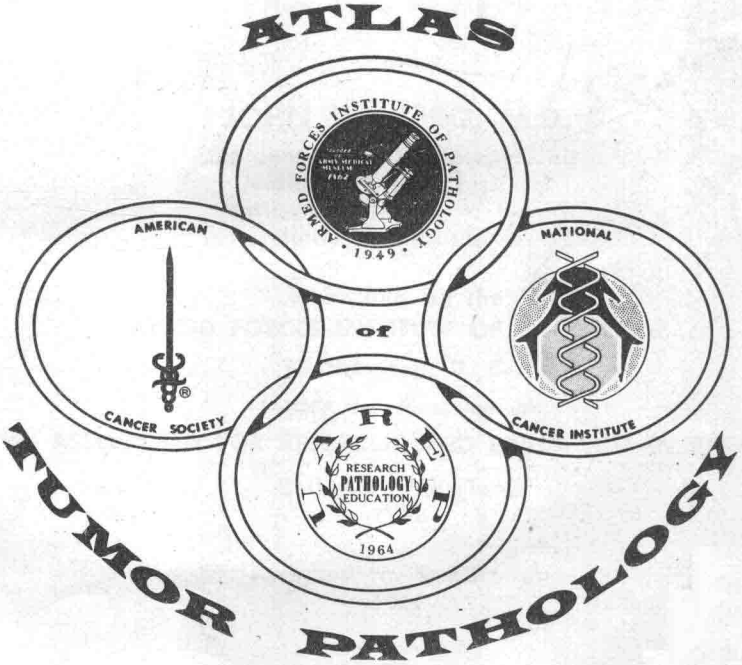

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ATLAS OF TUMOR PATHOLOGY

Second Series

Fascicle 2

TUMORS OF THE BREAST

by

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EDITOR'S NOTE

The Atlas of Tumor Pathology was originated by the Committee on Pathology of the National Academy of Sciences—National Research Council in 1947. The form of the Atlas became the brain child of the Subcommittee on Oncology and was shepherded by a succession of editors. It was supported by a long list of agencies; many of the illustrations were made by the Medical Illustration Service of the Armed Forces Institute of Pathology; the type was set by the Government Printing Office; and the final printing was made by the press at the Armed Forces Institute of Pathology. The American Registry of Pathology purchased the fascicles from the Government Printing Office and sold them at cost, plus a small handling and shipping charge. Over a period of 20 years, 15,000 copies each of 40 fascicles were produced. They provided a system of nomenclature and set standards for histologic diagnosis which has received world-wide acclaim. Private contributions by almost 600 pathologists have helped to finance the compilation of an index by The Williams & Wilkins Company to complete the original Atlas.

Following the preparation of the final fascicle of the first Atlas, the National Academy of Sciences—National Research Council handed over the task of further pursuit of the project to Universities Associated for Research and Education in Pathology, Inc. Grant support for a second series was generously made available by both the National Cancer Institute and the American Cancer Society. The Armed Forces Institute of Pathology has expanded and improved its press facilities to provide for a more rapid and efficient production for the next series. A new Editor and Editorial Advisory Committee were appointed, and the solicitation and preparation of manuscripts continues.

This second series of the Atlas of Tumor Pathology is not intended as a second edition of the first Atlas and, in general, there will be variation in authorship. The basic purpose remains unchanged in providing an Atlas setting standards of diagnosis and terminology. Throughout this new series, the term chosen by the Committee on Tumor Nomenclature of the International Union Against Cancer* is shown by an asterisk if it corresponds to the author's heading, or as the first synonym in italics if it differs from the author's first choice. Hematoxylin and eosin stained sections still represent the keystone of histologic diagnosis; therefore, most of the photomicrographs will be of sections stained with this technic, and only sections prepared by other technics will be specifically designated in the legends. It is hoped that in many of the new series a broader perspective of tumors may be offered by the inclusion of special stains, histochemical illustrations, electron micrographs, data on the biological behavior, and other pertinent information for better understanding of the disease.

The format of the new series is changed in order to allow better correlation of the illustrations with the text, and a more substantial cover is provided. An index will be included in each fascicle.

It is the hope of the Editor, the Editorial Advisory Committee, and the Sponsors that these changes will be welcomed by the readers. Constructive criticisms and suggestions will be appreciated.

Harlan I. Firminger, M. D.

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*Preferred terminology of Committee on Tumor Nomenclature and Statistics of the International Union Against Cancer. Springer-Verlag, Berlin, Heidelberg, New York, 1965.

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The text and illustrations, unless otherwise specified, were prepared from material from the files of the Pathology Department of the Memorial-Sloan Kettering Cancer Center. We thank Dr. Frank W. Foote, Jr., Chairman, Department of Pathology for permission for their use.

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Robert W. McDivitt
Fred W. Stewart
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TUMORS OF THE BREAST

INTRODUCTION

An interval of about 15 years has elapsed between the publication of the first fascicle on human breast cancer and the present volume. In the interim, substantial new information has been accumulated on various aspects of the problem. New data are available on extended surgical procedures; restricted surgical attack, such as simple mastectomy with or without x-ray therapy; chemotherapy concurrent with surgery; hormone addition or ablation for metastatic tumor; the matter of circulating tumor cells, genetics, and geography. Indeed, information is available on almost everything except how to cure more human breast cancers. Unfortunately, a patient with cancer of the breast today has just about the same outlook for cure as the patient of yesterday, given the same stage of disease at time of diagnosis, and assuming equal treatment facilities existed in both instances. Palliation, of course, has greatly improved.

The main purpose of the fascicle in the beginning was to show students and pathologists chiefly the microscopic forms of the disease in order to aid in the recognition of breast cancer, and to avoid the diagnosis of cancer for noncancerous conditions. Over the years it became apparent that the initial fascicle had been of benefit. This was seen from the many slides of breast lesions received from other laboratories in consultation. There has been a substantial decline in overdiagnosis of breast cancer, and less confusion associated with sclerosing adenosis, innocent papillomas of ducts, and various hyperplasias. Needless to say confusion has not vanished, and both over and underdiagnosis still exist, although generally, the level of diagnosis is much improved. The orientation of the new fascicle is somewhat different and for definite reasons. That difference is in placing increased emphasis on "early" lesions.

Lacking something new on the horizon for treatment of the patient with breast cancer, improvement in end results would seem to rest on increasingly early pathologic diagnosis. We should define what we mean by "early." Pathologists who look at a breast cancer cannot use the word "early" in the sense of time since one really knows little about the actual age or time sequence of lesions. We use it to describe a stage of disease in terms of the function of time of existence, but readily recognize that this is not measurable. No one has seen a beginning cancer and recorded its progress by time-lapse filming.

In describing a cancer, the words "small" and "early" are not synonymous to us. The designation of a "small" cancer depends on individual preference, and we know of no standard. To the authors, "early" means a cancer that is confined to ducts or lobules, or both, and nowhere is seen to be infiltrative.

Although the concept of in situ carcinoma is old, over the past 25 years it has received much attention because of the impact of technics for the cytologic detection of early phases of cancer, particularly carcinoma of the cervix, and disclosures which have resulted from efforts at histologic confirmation or denial of the cytologic interpretation. This search has resulted in the tendency on the part of pathologists to

recognize earlier and earlier changes on which a diagnosis of cancer may be made, a tendency which is both useful and dangerous owing to overenthusiasm. In these breast lesions, we have said that "early" means they are cytologically cancerous but still within the area of origin, that is, intraductal or intralobular. How long such a situation may be maintained is unknown, but it is highly probable that it may last for years or even decades. Acknowledging that it can last a long time does not mean that it invariably does. Conclusions of this sort rest upon evidence less satisfactory than true science should demand, but there is no means of sounder appraisal as yet. One cannot remove a section of breast, find an in situ carcinoma, and be certain that the infiltrative cancer found elsewhere in the same breast years later was there in an in situ form at the time of the initial excision. The mere fact that disease of this type is extremely apt to be multifocal gives support, of course, to the belief that it was there and has taken years to evolve. To sustain this fact, when the diagnosis is made on local excision and the remaining breast is studied after simple mastectomy, one almost always finds residual disease of the same type. Of course, one could speculate that the carcinogenic stimulus might reach the breast on more than a single occasion; thus, not all foci of in situ carcinoma need have existed simultaneously, or for that matter have developed at the same rate. However, in thinking about the time factor, we can draw analogies from cancers, such as cervical cancer, which can be seen and kept under easy and continued scrutiny and rebiopsied over the years. We strongly suspect that what we can observe in the cervix also occurs in the breast; that is, the phase preparatory to infiltration is long. How long, and how consistently long, we can only guess.

The present fascicle, like the first one, is an atlas and not a general treatise on mammary carcinoma. Illustrations may appear excessive; there is repetition but this is for a specific purpose. It affords the viewer an opportunity to compare confusing lesions, and aid in the distinction between benign and malignant, or disturbing patterns.

EPIDEMIOLOGY

The epidemiology of breast cancer has received much recent attention. The studies of Lilienfeld, Post, and Wynder and associates are particularly noteworthy. Despite the geographic, cultural, and genetic correlations that have been established, there is as yet, however, no identification of the major causative agents or situations equivalent to that of smoking and lung cancer.

The geographic occurrence is highly variable as can be seen from Figure 1 compiled by Segi and Kurihara*.

Countries with high rates tend to be affluent, such as Denmark, Canada, the United States, England, the Netherlands, and Switzerland. However, the incidence in Norway, Sweden, and Germany is only moderate. Elsewhere in Europe, Poland has the lowest apparent rate. France, Italy, and Finland previously had low rates which are now, however, rising steeply. Japan has the lowest well documented rate in the world. By comparison, the incidence recorded by Segi and Kurihara for other Orientals, such as the Chinese and Malaysians, would be considered moderate.

In India, the more Aryan and prosperous Parsees have the highest rate, although the disease is not rare in other groups. In Africa, the incidence in the Bantu and Ugandans is

*Redrawn from Figure 22, from Segi, M., and Kurihara, M. Cancer mortality for selected sites in 24 countries, No. 4, Department of Public Health, Sendai, Japan, 1966.

almost as low as in the Japanese, but in West Africa the disease is common, as it is in American Negroes. In Latin America, Chile reports a low incidence, as does Puerto Rico, while the rates in Columbia and Mexico are higher but still below most European rates.

Support for the concept that the geographic difference in incidence is in part cultural, rather than wholly racial, comes from studies of migrants made by Staszewski and Haenszel. Women from Italy, Poland, and Japan, who come to the United States, all show a substantial increase in breast cancer following the change in domicile.

Text Figure 1

TRENDS IN AGE-ADJUSTED DEATH RATES FOR MALIGNANT NEOPLASM OF BREAST (FEMALE), 1950-1951 TO 1962-1963

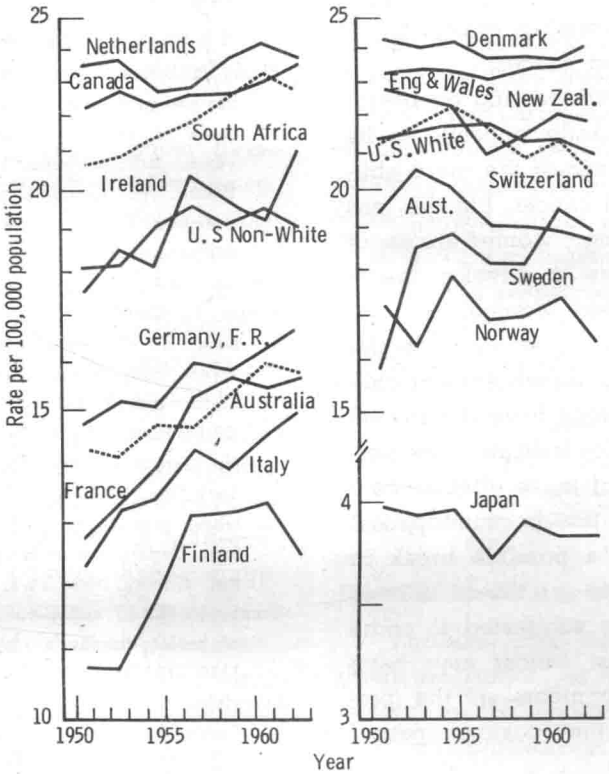

Figure 1. A.F.I.P. Atlas No. 67–1–129.

Little work has yet been published as to whether the approximate six fold geographical differences in incidence are associated with differences in histologic form or behavior. Cancers in Japan were reported as being histologically rather different from those in America, but the series was highly selective, and preliminary review of other sets of tumors in Japan does not confirm the reports. The breast cancer grading system for cancers in England, developed by Scarff and Bloom, as described in the paper of Bloom and Richardson, puts great weight on tubule formation in duct carcinomas, a feature far more prominent in their material than in current tumors in America. Reporting from Middlesex Hospital, the World Health Organization (WHO) reference center for

breast cancer, Thackray unofficially has said that he considers breast cancers from African Negroes particularly and recognizably anaplastic.

Within a given cultural region the population variables have less effect and the differences in incidence rates are smaller. For American women, the basic risk of ever developing breast cancer is now about 1 in 16 (Ferber and associates) but when there is a family history of breast cancer, this risk rises two to three times. A family history of other types of cancer does not appear to increase the risk of breast cancer.

The influence of childbearing on breast cancer incidence is exactly opposite to its influence on cervical cancer: the more children, the more cervical cancer, but the less cancer of the breast. Single women are about 75 per cent more prone to develop breast cancer than are married women. Among married women, the nulliparous have the highest rate; those who nursed several children without complications have the lowest rate. A number of studies indicate, however, that the manifestation of these effects seem limited to women in the postmenopausal period. This fact, and a possible break in the age-specific incidence and the death rates at about this age, have suggested to some investigators that breast cancer may have different causal environments in the premenopausal and in the postmenopausal periods.

Reported associations of breast cancer with other diseases are few and at times conflicting. In the study of de Waard and associates, breast cancer patients were found to have excess hypertension, obesity, and diabetes, but these associations are weak. Ederer found more definite association between breast, endometrial, and ovarian cancer. In contrast, the reported association with colon carcinoma seems largely the coincidence of two diseases, possibly accentuated by their common tendency to occur more frequently in Jewish women. Hypothyroidism has been suggested to have protective effect against breast cancer, but it has also been said that breast cancer is more frequent in women with thyroid "disease" (Humphrey and Swerdlow).

There is no epidemiologic evidence to support an association between benign breast disease and carcinoma other than that discussed in the section Precancerous Lesions (p. 14).

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HOST RESISTANCE

In theory, the growth and spread of cancer must be the result of the interaction between the cancer cells and their host, so that prognosis is a function of both host resistance and tumor aggressiveness. In practice, as yet, we know nothing tangible about such interplay in humans. We cannot, of course, see the best examples of host resistance because this means the failure of cancer cells to survive, let alone multiply. Just the fact that a cancer has reached clinical size is a sign of inadequate or absent host resistance, yet it is only these cancers that we study.

Antibodies against breast cancer have been found, but we are not aware of evidence that the presence of such antibodies are correlated with better than average prognosis. A pattern of increased histiocytosis in lymph nodes has been suggested as an indication of good prognosis but to our knowledge there has been no elucidation of a resistance mechanism explaining this pattern. It could be simply an early stage of passive lymph node change in response to the presence of cancer in the area drained. Tumors bordered by plasma cells have a better than average cure rate, but the patient's survival is no better, if not cured. Although this pattern resembles the homograft rejection response, it has not been connected with any defense mechanism nor has it been shown that these circumscribed tumors do better than similarly circumscribed tumors with no margin of plasma cells. It is still by examination of the tumor itself, in the breast and elsewhere, that the expected growth rate, likelihood of metastases beyond the axilla, and prognosis are determined.

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SEX CHROMATIN AND PROGNOSIS

It has been suggested that the sex chromatin incidence may be something of a prognostic guide in breast cancer. Wacker and Miles studied 50 cases in our laboratories for the presence or absence of sex chromatin. They found a linear correlation between sex chromatin incidence and length of survival for patients dying within eight years of initial treatment. Patients who survived beyond eight years had, as a group, a significantly higher sex chromatin incidence. It is suspected that low sex chromatin incidence is related to increasing anaplasia rather than a type of sex reversal.

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BILATERALITY OF BREAST CARCINOMA

Robbins and Berg recently reported upon the subject of second primary breast cancer in the contralateral breast, basing their interpretation on pathologic criteria, the most important being the existence of in situ change contiguous with the second tumor. Such changes occurred in all but 7 of the 91 cases with second primary breast cancers in a group of 1,458 women who entered the study during the years 1940–1943. The study, including the follow-up of these cases, covered a 20-year period. In the 7 cases without in situ change, the tumors accepted were either quite different histologically from the tumor of the first breast; or they were