Breast Cancer

Epidemiology, Endocrinology,
Biochemistry
and Pathobiology

Helmuth Vorherr, M.D.

Preface

Definition of risk factors for breast cancer, exploration of the disease's etiology and measures for its possible prevention represent a major challenge. Breast carcinogenesis seems to involve genetic, environmental, hormonal and immunological mechanisms. On the other hand, some conditions, such as ovariectomy, early pregnancy or lactation appear to provide protection against breast cancer.

In recent years, tumor pathobiology has been related to local and systemic metabolic, hormonal, biochemical and immunological changes. One of the most important clinical aspects of the hormonal status of breast cancer tissue appears to be the determination of receptors for estrogens and various other hormones, yielding information for the prognosis and choice of treatment of recurrent disease.

At this point, uncertainty exists regarding the role of abnormalities in the metabolism of endogenous steroid hormones in the development of breast cancer. Also, it is not clear whether administration of estrogens for hormone replacement therapy provides a carcinogenic risk to the breast. Extensive efforts are now being made to develop *in vitro* and *in vivo* models for studies in regard to etiology, tumor pathobiology, immunology, diagnosis and treatment of breast cancer. Besides immunotherapy, even immune prophylaxis of breast cancer, in analogy to childhood leukemia, has been proposed.

In this monograph an effort has been made to present and integrate the most important data on epidemiology, virology, biochemistry, endocrinology and immunology of breast cancer and to evaluate their relevance for the advancement of knowledge in the field of breast cancer, even though it is not always possible to reconcile contradictory reports found in the literature.

At the end of each chapter is a summary of the quantity and quality of data, their potential impact on laboratory and clinical research, and benefits for the breast cancer patient.

This monograph on breast cancer may be considered an extension of *The Breast: Morphology, Physiology, and Lactation* (Academic Press, New York, 1974), which deals with the normal breast.

It is hoped that this book will stimulate investigators and physicians concerned with the subject of breast cancer to search for new and more effective ways to deal with the problem.

Introduction

Breast cancer is the most predominant malignancy with the highest mortality rate in women. Whereas more than 20 risk factors may have been defined, conditions also seem to exist which may protect against breast cancer. In recent years, hormonal risk factors of breast cancer have been studied extensively, and they have been correlated with the availability of estradiol and estrone. Mechanisms protecting against breast cancer are thought to be due to mitotic rest of mammary epithelium, as encountered during pregnancy and lactation and to the action of estriol and progesterone opposing the "carcinogenic" estradiol and estrone.

Besides genetic factors, environmental, dietary, hormonal, biochemical and immunological mechanisms have been studied for their relevance in the pathobiology of breast cancer. Attempts have been made to define and utilize the measurement of hormonal, biochemical, and immunological parameters in malignant tissue and blood for the elucidation of the disease process, possibly serving as clues for early diagnosis and for the selection of the treatment modality and prognosis of the course of the disease.

Some progress has apparently been made in recent years by *in vitro* measurement of estrogen receptors in breast cancer tissue for selection of patients who might benefit from endocrine therapy. On the other hand, the success of combination cytotoxic polychemotherapy seems to outweigh the benefits achieved with estrogen receptor assays and endocrine therapy. Unfortunately, despite all the efforts and frequently reported "breakthroughs" in the fight against breast cancer, the mortality rate has not changed over the last 50 years.

Contents

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1. Mortality and Incidence Rates of Breast Cancer

MORTALITY RATES

The breast is the most common site of malignancy in women, and the death rate from breast cancer (28 per 100,000 female population) has been constant for over 45 years (Shapiro et al., 1968; Feinleib and Garrison, 1969; Black, 1970; Miller, D.G., 1976) (fig. 1.1). The overall 5-year survival rates for

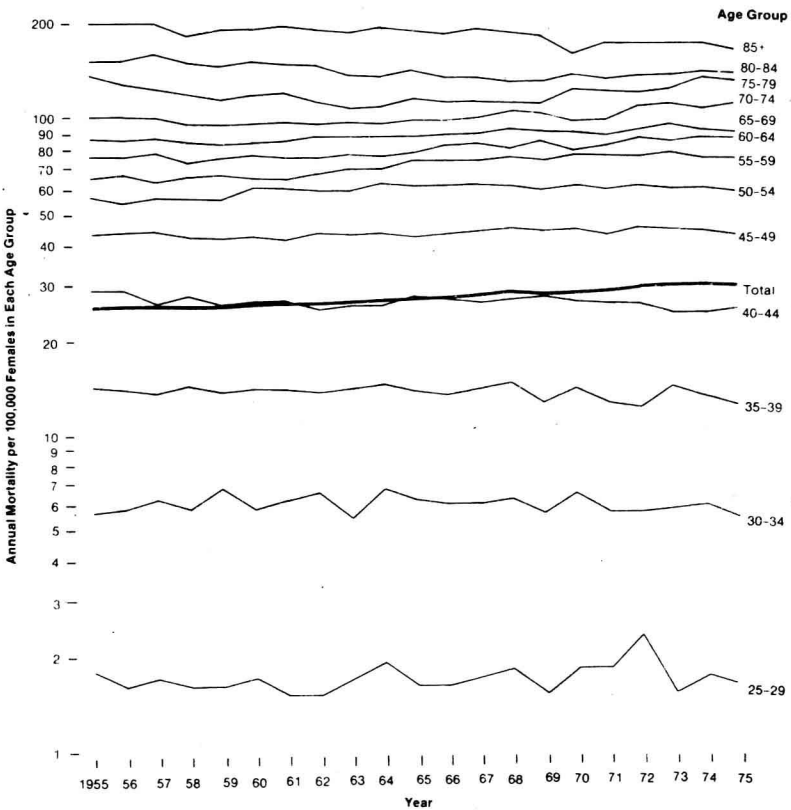

Fig. 1.1. Mortality from breast cancer in the United States, 1955–1975. Illustrated are the breast cancer mortality rates for females, age 25 and older, by 5-year age groups for the United States between 1955 and 1975. Although a trend toward lower mortality of breast cancer among women under age 45 is noticed for the last 5 years, essentially in all age groups mortality from breast cancer remains unchanged. (From Department of Medical and Public Affairs, George Washington University Medical Center, 1977, with kind permission.)

all stages of breast cancer of 62% and 47% for white and black American females, respectively, have not changed over this period (Seidman, Silverberg, and Holleb, 1976). Breast cancer is the cause of death for 20% of American women who die from malignant disease (Shapiro et al., 1968; Silverberg, 1977). For American women, the probabilities at birth of eventually developing and dying of breast cancer are 8% and 3%, respectively (Seidman, Silverberg, and Bodden, 1978). It has been estimated for the years 1976, 1977, and 1978 that 88,000, 89,000, and 90,000 new breast cancer cases, respectively, occurred and that approximately 33,000 patients were expected to die from breast cancer

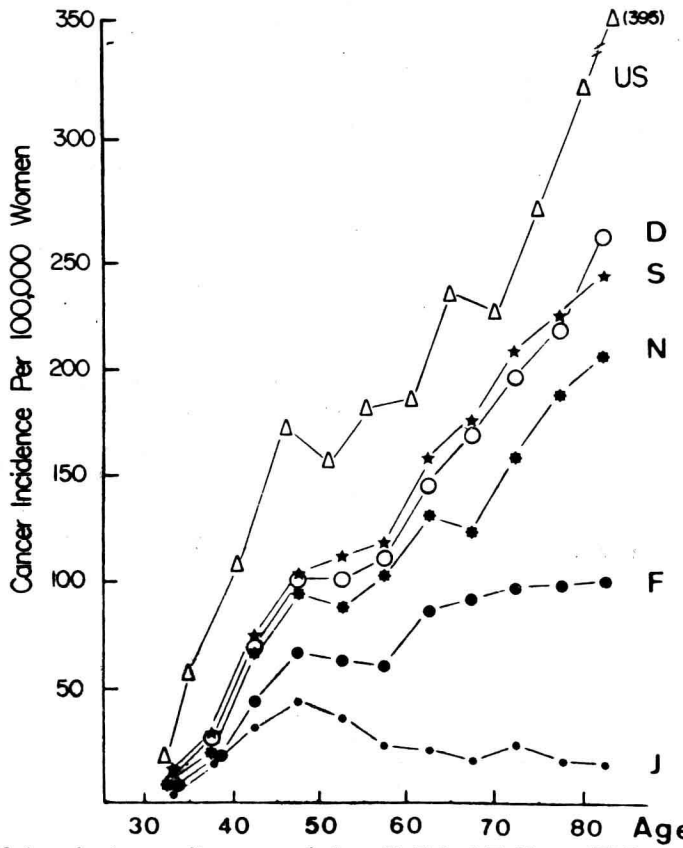

Fig. 1.2. Age-related curves of breast cancer in Japan (J), Finland (F), Norway (N), Denmark (D), Sweden (S), and the United States (US).
After the age of 35, a rather steep rise in breast cancer incidence is observed up to the age of 45 to 50 years, followed by a temporary plateau or even a slight decrease. Beyond the age of 55 to 60, with the exception of Japanese women (decline) and Finnish women (moderate rise), a steep rise of the incidence curves for breast cancer again becomes apparent. Note the pronounced difference in incidence rates between American and Japanese women. (Adapted from de Waard, 1969, with kind permission.)

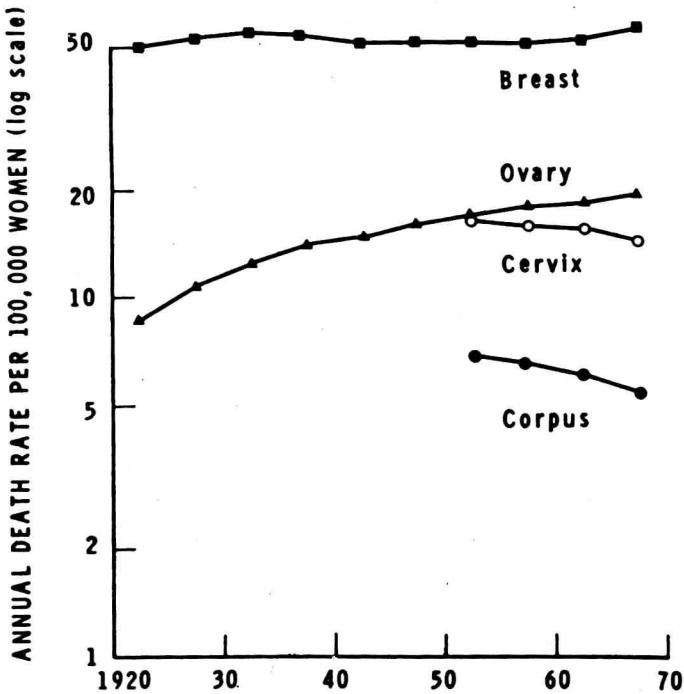

Fig. 1.3. Mortality from cancers of breast, ovary, cervix, and corpus uteri. Breast cancer mortality rates have remained constant during the last 50 years. Mortality from ovarian cancer shows a progressive increase, whereas death rates from cancer of cervix and endometrium have declined steadily since 1950. (From Doll, 1975, with kind permission.)

annually in the United States (Seidman et al., 1976; Silverberg, 1977; Silverberg, 1978). For the year 1979, 106,000 new cases may occur, and 34,200 women are expected to die from breast cancer (Silverberg, 1979). In contrast to the relatively high death rate in the United States, breast cancer mortality in Thailand, El Salvador, Egypt, and Japan is only 0.9, 1.4, 3.0, and 4.4 per 100,000, respectively (Silverberg, 1977).

INCIDENCE RATES

Wynder and Gori (1977) reported breast cancer incidences of 62.3 and 11.0 per 100,000 (incidence ratio: 5.6) for American and Japanese women, respectively (fig. 1.2). Conversely, the incidences of stomach cancer were 6.8 and 44.7 per 100,000 (incidence ratio: 0.1) for American and Japanese women, respectively (Wynder and Gori, 1977). Whereas the incidence rates of cervical and endometrial cancer declined steadily during the last three decades (fig. 1.3), the incidence rate of breast cancer shows little change for white females (70.0

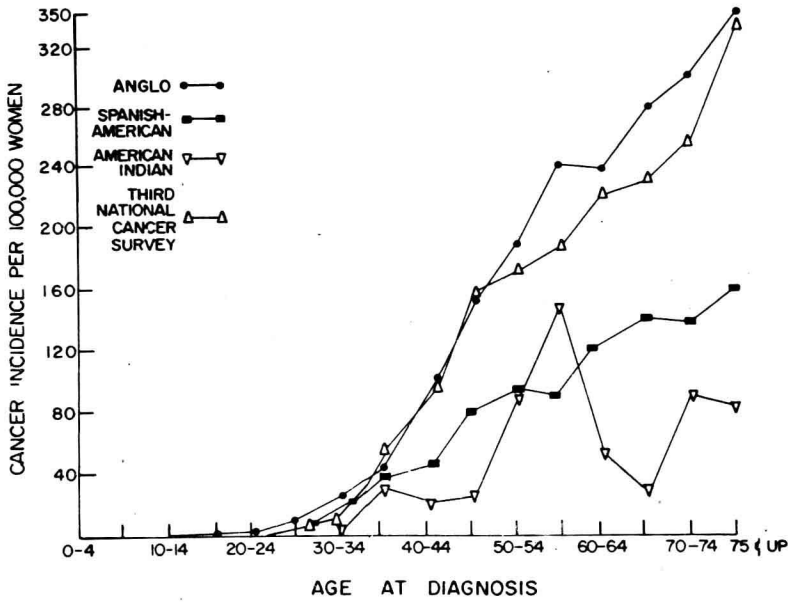

Fig. 1.4. Age-specific incidence rates for breast cancer for Anglos, Spanish-Americans, and American Indians of New Mexico. The breast cancer statistics for the years 1969 to 1974 in New Mexico show that the age-adjusted rate for breast cancer incidence in Anglos (86 per 100,000; total cases: 1,385) is almost double that of Spanish-Americans (42 per 100,000; total cases: 317) and approximately triple that of American Indians (26 per 100,000; total cases: 31). The fluctuations in the age-specific curve for American Indians is due to the small number of total cases. (From C. Key and D. Kutvirt of the New Mexico Tumor Registry, personal communication, 1977.)

and 72.5 per 100,000 population for the years 1947 and 1968, respectively); for black North American females a trend has been observed toward an increase in breast cancer incidence: from 47.8 per 100,000 in 1947 to 60.1 per 100,000 population in 1969 (Seidman et al., 1976). But Shapiro et al, (1968) did not observe a difference in breast cancer incidence between whites and nonwhites. In Spanish-Americans and American Indians of New Mexico, the breast cancer incidence is much lower than in "Anglos" (fig. 1.4). It has been reported, however, that breast cancer incidence in women under age 55 has increased approximately 45% since 1935, whereas breast cancer rates above age 55 have remained constant (Feinleib and Garrison, 1969). However, *Population Reports* (Department of Medical and Public Affairs, George Washington University, 1977) (fig. 1.5) indicate a trend toward increasing breast cancer incidence among women over age 35. During the years 1947 to 1969, 3.6% and 26% increases of the incidence of breast cancer in the United States have been reported for Caucasian and Negro women, respectively (Petrakis, 1977).

The increase in incidence and mortality rates of breast cancer in American

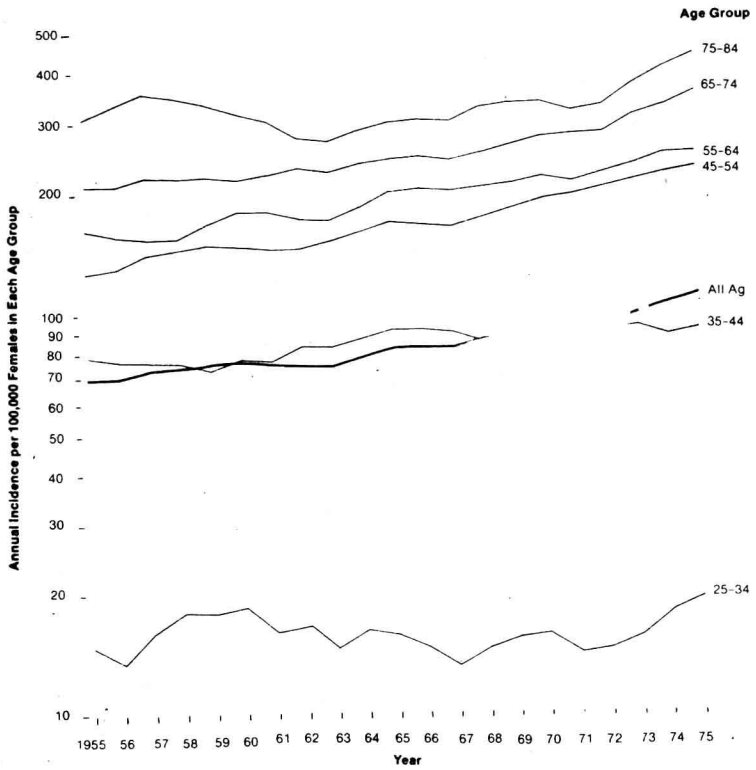

Fig. 1.5. Incidence of breast cancer in Connecticut (USA), 1955–1975. Illustrated are the incidence rates of breast cancer for females, age 25 to 84, by 10-year age groups, using 3-year moving averages. A trend toward increasing breast cancer incidence among women over the age of 35 in Connecticut is apparent. Data for 1975 are provisional. (From Department of Medical and Public Affairs, George Washington University Medical Center, 1977, with kind permission.)

and English women, mainly between the age of 45 and 64, has been explained by a decrease in fertility; but an increase in fat and meat consumption and other unknown factors may also have contributed (Armstrong, 1976). On the other hand, the increase of breast cancer—"some 10 per cent in the past two decades"—has been explained as being related to changing diagnostic criteria (Wynder, Bross, and Hirayama, 1960; Black, 1970; Fox, 1979). In 1941 the entity of mammary lobular carcinoma *in situ* was described, and the inclusion of this nonlethal lesion in the category of breast cancer "would have the effect of increasing the overall incidence rate 5 to 10 per cent and the premenopausal rate some 30 per cent without a corresponding increase in death rate" (Black, 1970).

Whereas Senn (1978) stated that the incidence of breast cancer showed

only a slight increase, especially in premenopausal women, Fox (1979) reported that it increased by 18% between 1935 and 1965 and by 50% between 1965 and 1975 but that the mortality rates remained unchanged. Fox (1979) explained the increase in the apparent incidence of breast cancer as being related to changes of diagnostic criteria, including ambiguous cases in which the lesions diagnosed as cancer rarely or never make the transition to local or systemic spread. Minimal breast cancer, i.e., carcinoma *in situ* and invasive cancer smaller than 1 cm in diameter, may often be subject to differences of opinion among pathologists, because the demarcation between severe hyperplasia and carcinoma *in situ* "represents the interpretive science or the art of pathology" (Holleb, 1979). Nevertheless, inclusion of some relatively benign lesions in the number of breast cancer incidents should lead to a decrease in the mortality rate of breast cancer patients. This has not been observed. On the other hand, if a true increase in the incidence of breast cancer is assumed, but the mortality rates have remained the same, it would indicate that indeed the tumor pathobiology in some patients is more "benign" and/or that early diagnosis and therapy of breast cancer have improved.

The frequency of breast cancer compared to all other cancers is especially high: 26%. For dogs it is 13% and for cats 5%; mammary cancer accounts for less than 1% of all cancers in cattle and horses (Klein and Smith, 1977).

SUMMARY

The probability at birth of an American female dying eventually from breast cancer is 3% or more. Approximately 28 per 100,000 women in the United States will die annually from breast cancer. Little change has been observed over the years in mortality and incidence rates of breast cancer. A recent trend toward a moderate increase in breast cancer incidence has been explained by decreasing fertility, increase in fat and meat consumption, and changing diagnostic histological criteria. In conclusion it may be stated that breast cancer mortality has not changed substantially during the last four to five decades, indicating the lack of diagnostic and/or therapeutic progress.

2. Breast Carcinogenesis
Etiology, Epidemiology, Tumor Pathobiology

CARCINOGENIC MECHANISMS

Cancer may be considered primarily "a genetic disease at the cellular level" because irreversible changes in the cellular hereditary material occur in the development of a cancer cell; hereditary, environmental, and other factors may influence the probability of such changes (Strong, 1977). Accordingly, carcinogenesis may involve genetic predisposition, physical and chemical causes, viruses and chronic infection, medication, hormonal stimuli, and decreasing immunocompetence due to aging (Fox, 1978). Chemical carcinogens have been defined as (a) proximate carcinogens, effective in their immediate chemical form; (b) procarcinogens, which require conversion into carcinogens; and (c) cocarcinogens, which require the presence of another chemical substance for induction of cancer (Kolbye, 1976).

Cancer may be induced (a) by a primary (initiating) carcinogen, i.e., by a reactive carcinogenic molecule (chemical carcinogen) "arising from the molecular modification of a particular substance" coming in direct contact with the cell or within it; or (b) by a secondary (promoting) carcinogen, i.e., a particular substance (virus) that transforms another molecule, macromolecule, or cellular unit into a carcinogen (Kolbye, 1976). Initiating agents may induce cancer by a single exposure without apparent threshold dose, provoking an irreversible electrophilic cellular reaction that results in mutagenesis; but promoting agents cannot cause such action (Weinstein, 1978).

BREAST CARCINOGENESIS

Breast cancer is considered a multifactorial disorder, where (a) genetic constitution (genetically transmitted susceptibility); (b) endogenous hormone imbalance (estrogens, progesterone, androgens, prolactin); (c) oncogenic factors (viruses, diet, obesity, glucose intolerance); (d) environmental conditions, such as estrogen intake, cigarette smoking, chemical carcinogens in food (food additives), drinking water, and air, may all play a role (figs. 2.1 and 2.2). It is thought that when blood levels of free fatty acids, insulin, cholesterol, and triglycerides rise, as in response to stress, preg-