

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

Acknowledgments	3
Preface	3
Introduction	5
1. Mortality and Incidence Rates of Breast Cancer	3
Mortality Rates	3
Incidence Rates	5
Summary	8
2. Breast Carcinogenesis: Etiology, Epidemiology, Tumor Pathobiology	9
Carcinogenic Mechanisms	9
Breast Carcinogenesis	9
Epidemiology of Breast Cancer	12
Trauma, Temperature of Environment, Psychosomatic Changes, and Stress	20
Carcinogenesis in Relation to Cell Cycle: Tumor Pathobiology	21
Summary	24
3. Breast Cancer in Relation to Age and Endocrine Status	25
Age	25
Endocrine Status	28
Summary	35
4. Breast Cancer in Relation to Diet, Overnutrition, and Obesity: Hormonal, Immunological, and Environmental Aspects	37
Diet and Risk of Breast Cancer	38
Overnutrition and Obesity in Relation to Breast Cancer	45
Diet and Mammary Tumorigenesis in Mice and Rats	51
Summary	53
5. Potentially Predisposing Conditions for Breast Cancer	55
Hereditary Predisposition to Breast Cancer	56
Nonfamilial Risk Factors of Breast Cancer	66
Summary	79
6. Conditions Potentially Protective Against Breast Cancer	81
Bilateral Ovariectomy	81
Pregnancy and Risk of Breast Cancer	82

Pregnancy Coexisting with Breast Cancer	85
Pregnancy Following Treatment for Breast Cancer	89
Lactation and Risk of Breast Cancer	89
Mechanisms of Pregnancy Potentially Protective against Breast Cancer	95
Mechanisms of Lactation Potentially Protective against Breast Cancer	105
Summary	105
7. Prolactin in Relation to Breast Cancer	107
Breast Cancer Ontogenesis and Prolactin Profile	107
Endogenous Factors Promoting Prolactin Secretion and Their Re- lationship to Breast Cancer	108
Prolactin as a Potential Risk Factor in Breast Cancer	109
Hyperprolactinemia and Risk of Breast Cancer	111
Prolactin Blood Levels in Breast Cancer Patients	112
Role of Prolactin in Breast Cancer	113
Inhibition of Prolactin Secretion and Breast Cancer Remission	117
Medicamentous Depression of Prolactin Secretion as "Pro- phylaxis" against Breast Cancer	118
Summary	119
8. Prolactin in Relation to Mammary Carcinoma of Rodents	120
The Role of Normoprolactinemia in Mammary Tumorigenesis	120
Prolactin: Chemical Carcinogen Interactions	121
Prolactin and Estrogen Receptors of Mammary Tumors	121
Hyperprolactinemia and Mammary Tumorigenesis	122
The Role of Prolactin-Estrogen Interaction in Mammary Tumori- genesis	122
Suppression of Prolactin Secretion and Mammary Tumorigenesis	123
Endocrine Ablation and Mammary Tumorigenesis	124
Summary	124
9. Thyroid Hormone in Relation to Breast Cancer	126
Hypothyroidism and Breast Cancer	126
Thyroid Hormone Replacement Therapy and Risk of Breast Can- cer	130
Hyperthyroidism and Risk of Breast Cancer	131
Effect of Thyroid Hormone on Breast Tissues and Sex Steroid Activity	131
Thyroid Abnormalities in Breast Cancer Patients	132
Thyroid Cancer in Association with Breast Cancer	134
Thyroid Hormone Treatment of Breast Cancer	134
Summary	135

10. Sex Steroids in Relation to Breast Cancer	136
Normal Premenopausal Women	136
Normal Postmenopausal Women	160
Endogenous Female Sex Steroids and Risk of Breast Cancer	167
Benign Breast Disease	183
Female Sex Steroids in Young Women with a Family History of Breast Cancer	185
Female Sex Steroids in Relation to Breast Cancer	186
Summary	199
11. Androgenic Steroids in Relation to Breast Cancer	201
Normal Premenopausal Women	201
Normal Postmenopausal Women	204
Normal Premenopausal and Postmenopausal Women: Urinary Excretion of 11-Deoxy-17-Osteroids (17-Ketosteroids)	207
Urinary 17-Ketosteroid Excretion in Japanese and Caucasian Women	208
Obesity: Adrenocortical Function; Effect of Starvation	208
Benign Breast Disease: Plasma Levels and Urinary Excretion of Androgenic Steroids	210
Androgenic Steroids in Relation to Breast Cancer	211
Summary	215
12. Adrenal and Ovarian Steroids in Relation to Diagnosis, Therapy, and Prognosis of Breast Cancer	217
Androgens	217
Factors Limiting or Invalidating the Clinical Usefulness of An- drogen Determinations	224
Estrogens and Progesterone	225
Summary	226
13. Melatonin, Growth Hormone, Insulin, and Glucocorticosteroids in Relation to Breast Cancer	228
Melatonin	228
Growth Hormone and Insulin	228
Glucocorticosteroids	229
Summary	231
14. Metabolic Activity, Biochemical Tissue Profile, and Markers of Breast Cancer	233
Metabolic Activity	233
Biochemical Tissue Profile in Breast Cancer	236
Biochemical Markers of Breast Cancer in Blood and Urine	241
Summary	246

15. Receptors of Normal and Neoplastic Mammary Epithelium	247
Estrogen Receptors	247
Progesterone Receptors	274
Androgen Receptors	276
Glucocorticoid Receptors	277
Prolactin Receptors	278
Insulin and Growth Hormone Receptors	278
Estrogen, Progesterone, and Androgen Receptors in Mammary Carcinomas of Rats and Mice	279
Summary	280
16. Exogenous Estrogens and Risk of Breast Cancer	282
Estrogen Medication and Increased Risk of Breast Cancer	282
Diethylstilbestrol Treatment during Pregnancy and Risk of Breast Cancer	285
Estrogen Medication Not a Cause of Breast Cancer	285
Estrogen Medication: "Prophylaxis" against Malignancy?	285
Estrogen-Progestin Combination in Relation to Benign and Ma- lignant Mammary Neoplasia	286
Estrogen Replacement Therapy in Postmenopausal Women	294
Concluding Comments on Estrogens and Risk of Breast Cancer: Problems of Evaluation	328
Summary	330
17. Estrogens and Mammary Carcinoma in Laboratory Animals	331
Estrogens and Mammary Carcinoma in Laboratory Rodents	331
Canine Mammary Cancer	334
Summary	335
18. Diagnosis of Breast Cancer	337
Clinical Signs and Symptoms and Localization of Breast Can- cer	337
Mammography	337
Thermography, Angiography, and Ultrasound	342
Aspiration Biopsy	342
Cytology of Breast Secretions	343
Immune Diagnosis of Breast Cancer	343
Summary	346
19. Pathobiology of Breast Cancer	347
Interrelationship between Benign and Malignant Breast Dis- ease	347
Prognosis and Pathobiology of Breast Cancer	348
Immunology of Breast Cancer	364
Summary	373

20. Treatment of Primary and Recurrent Breast Cancer	374
Primary Treatment	374
Secondary Treatment	383
Summary	407
21. Breast Cancer: Present Status and Future Outlook	409
Etiology of Breast Cancer	409
Progress in the Treatment of Breast Cancer	410
Prevention and Eradication of Breast Cancer	411
Early Diagnosis of Breast Cancer and Prolongation of Survival . .	412
Is Breast Cancer A Predetermined Fatal Disease?	412
Future Outlook and Conclusions	413
References	415
Index	467

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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

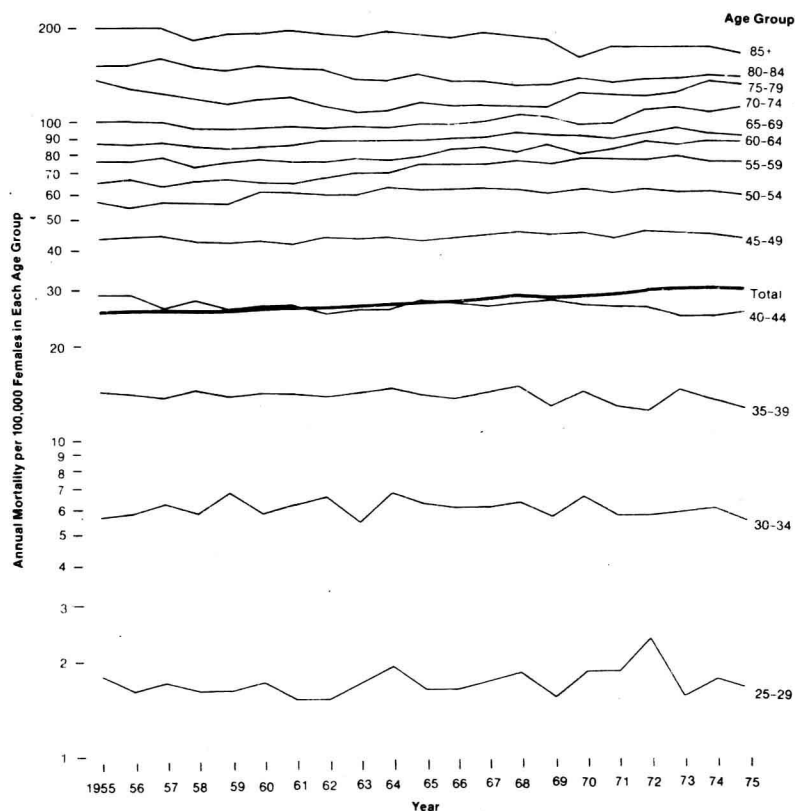


Fig. 1.1. Mortality from breast cancer in the United States, 1955-1975. Illustrated are the breast cancer mortality rates for females, age 25 and older, by 5-year age groups for the United States between 1955 and 1975. Although a trend toward lower mortality of breast cancer among women under age 45 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

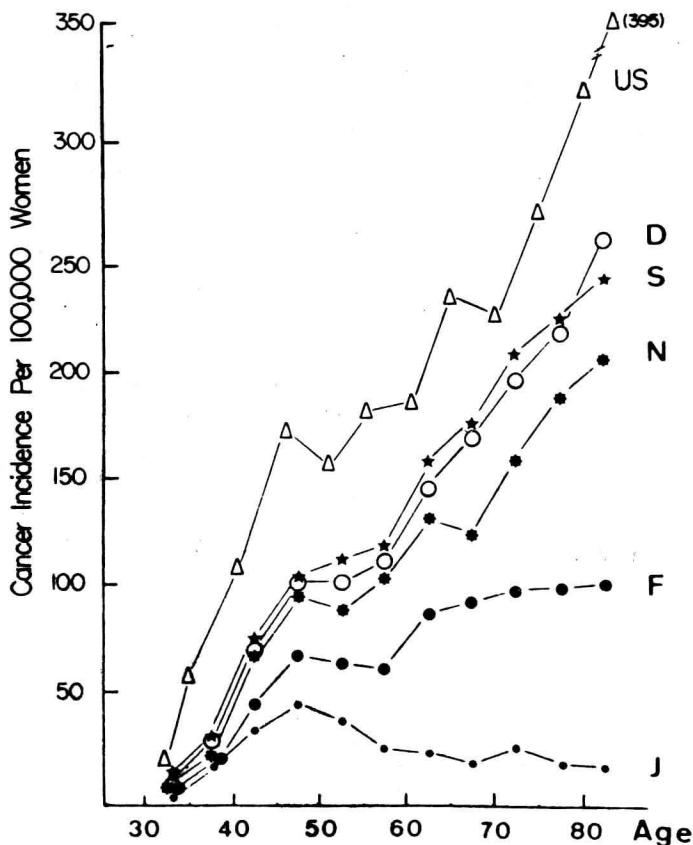


Fig. 1.2. Age-related curves of breast cancer in Japan (J), Finland (F), Norway (N), Denmark (D), Sweden (S), and the United States (US).

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.)

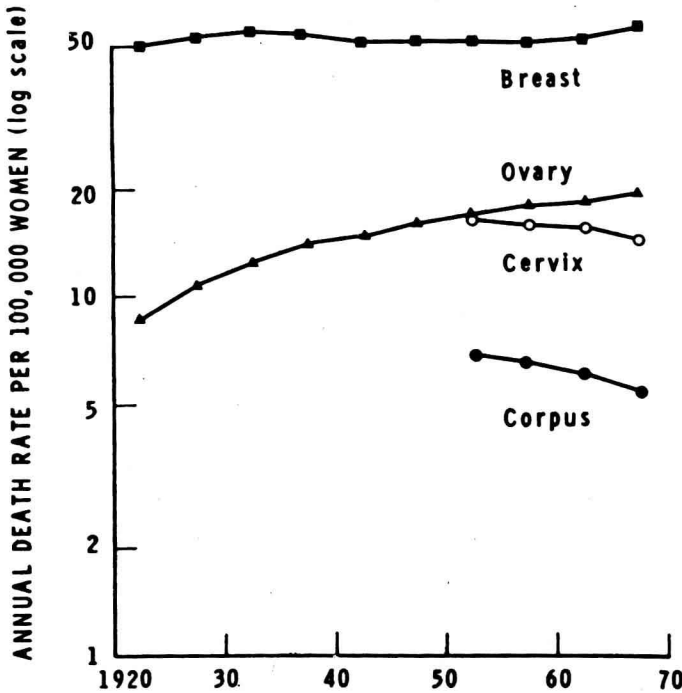


Fig. 1.3. Mortality from cancers of breast, ovary, cervix, and corpus uteri. Breast cancer mortality rates have remained constant during the last 50 years. Mortality from ovarian cancer shows a progressive increase, whereas death rates from cancer of cervix and endometrium have declined steadily since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

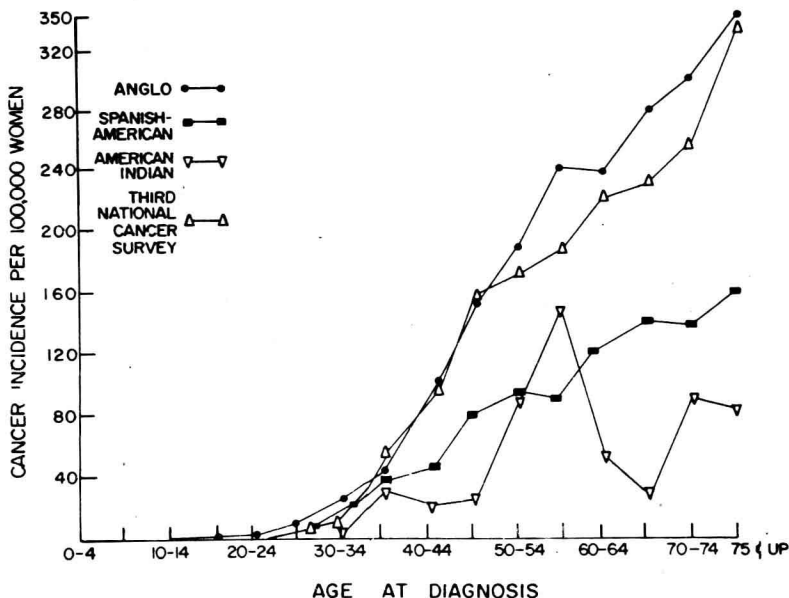


Fig. 1.4. Age-specific incidence rates for breast cancer for Anglos, Spanish-Americans, and American Indians of New Mexico. The breast cancer statistics for the years 1969 to 1974 in New Mexico show that the age-adjusted rate for breast cancer incidence in Anglos (86 per 100,000; total cases: 1,385) 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

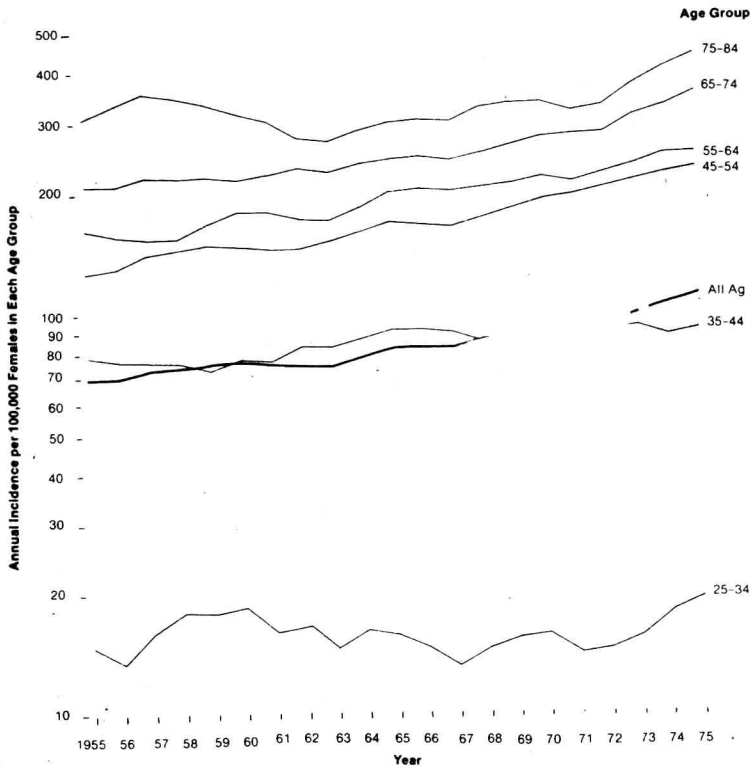


Fig. 1.5. Incidence of breast cancer in Connecticut (USA), 1955-1975. Illustrated are the incidence rates of breast cancer for females, age 25 to 84, by 10-year age groups, using 3-year moving averages. A trend toward increasing breast cancer incidence among women over the age of 35 in Connecticut is 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-