CARCINOMA OF THE BREAST
DIAGNOSIS AND TREATMENT

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Preface

This book attempts to present the many facets of breast carcinoma diagnosis and treatment in a single, readable source. While several books deal separately and exhaustively with the various topics included here, there is also a real need for one book designed to present all of the topics in some detail and to stimulate further reading as necessary.

The contributors to this volume are all recognized authorities in their respective fields. The chapter on psychological aspects of breast cancer by Christopher Gates and the chapter on biochemical markers by Nelson Burstein are unique in a book on breast cancer.

It is our hope that this book will provide a complete overview of breast carcinoma for the senior medical student, intern, and resident, all of whom most certainly will deal with this disease during their careers.

C. J. D.
R. E. W.

Carcinoma of the Breast

Notice

The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards for usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Contents

Jennifer L. Kelsey

1. Epidemiology of Breast Cancer in Women

Breast cancer is a major public health problem for women in the United States and other Western countries. In the United States, the annual age-adjusted incidence rate is about 85 per 100,000 women, and the age-adjusted mortality is about 28 per 100,000 women [154]; each year more than 100,000 women are diagnosed as having breast cancer, and about 30,000 deaths are attributable to it. It has been estimated [187] that 1 in every 14 women in the United States will develop breast cancer at some time during her life. Although mortality has remained relatively constant for many years, incidence rates have been increasing over the past two decades [10, 45].

Demographic Characteristics of Cases

In the United States and other Western industrialized countries, incidence rates for breast cancer increase rapidly with age until about 45 to 50 years of age; after this they continue to increase but at a slower rate [57]. Whites are affected somewhat more frequently than blacks [184]; Jews are affected more frequently than non-Jews [144, 184]; and women in upper social classes are affected more frequently than women in lower social classes [41, 55]. Women who have never been married are at greater risk than women who have been married, and nulliparous women are at higher risk than women who have borne children [95, 110, 144]. Within the United States, women living in urban areas are more likely to develop breast cancer than those in rural localities, and rates are higher in the North than in the South [22].

About 1 percent of breast cancer cases have simultaneous primary tumors in both breasts [23]. Unilateral tumors occur more frequently in the left breast than in the right breast, with the ratio of tumors in the left breast to the right ranging from 1.05 to 1.20 in various studies [62, 115]. Although the excess on the left side has been reported in many countries and in different racial groups, the reason for this excess is not known.

International Variation

In general, low incidence rates and mortality for breast cancer have been reported in most Asian and African countries, while intermediate rates have been found in southern European and South American countries, and high rates occur in North American and northern European countries [52]. It is of further interest that in most North American and northern European countries, incidence rates for breast cancer increase over the entire age span, with a somewhat less rapid rate of increase with age after 45 to 54 years of age than before (see Fig. 1–1). In countries with intermediate incidence rates and mortality, the incidence rates tend to plateau after about 50 years of age. In countries in which the risk for breast cancer is low, such as Japan, incidence rates actually decline after 50 years of age [49].

It has also been reported [121] that among migrants to Israel, the shape of the age-specific incidence curve for Jews born in Europe is similar to the North American–Northern European curves, while among Asian- and African-born immigrants, the incidence rates do not increase after age 50 years. Figure 1–1 shows that in Iceland incidence rates for breast cancer have increased markedly during this century. While this increase has been taking place, the shape of the age-specific incidence curve in that country has changed from that of the "low-risk" countries to that of the "high-risk" countries [19].

Studies of Japanese-American women have indicated that there is a gradual increase in breast cancer incidence rates among descendants of migrants to Hawaii or to the mainland of the United States. Rates begin to approach those of the United States after two or three generations [31]. This suggests that environmental factors rather than genetic variables are largely responsible for the marked international differences in incidence rates.

A high-calorie or high-fat diet is one environmental factor whose distribution corresponds to the difference in incidence rates from one country to another and from one time period to another. Consistent with the role of diet is the finding that, at least in the Netherlands and Japan, incidence rates in women of lighter-than-average weight tend to plateau or decrease after age 50 to 55 years, while incidence rates in heavier women continue to increase with age [50] (see Fig. 1–1). From these data, it was concluded that perhaps half the difference in inci-

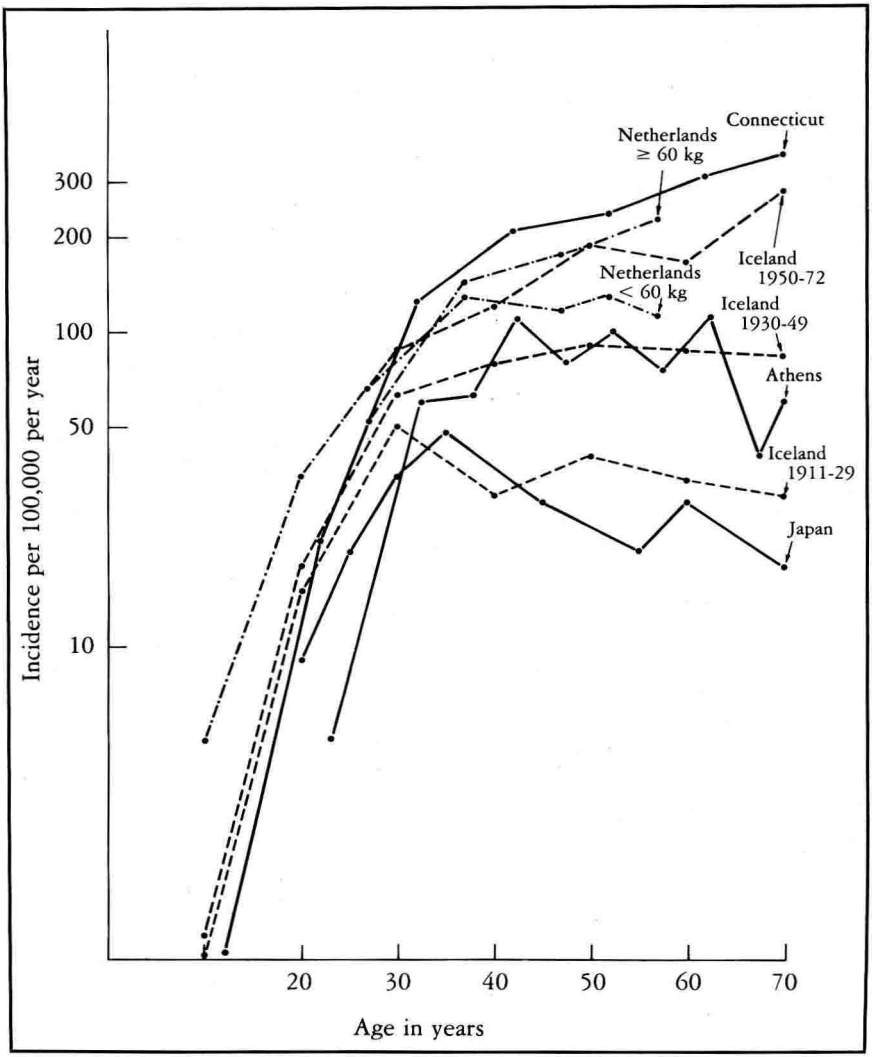

Figure 1–1. Age-specific incidence rates for breast cancer. *Solid lines:* Connecticut, USA, 1970–1974 [45]; Athens, Greece, 1966–1967 [112]; Miyagi Prefecture, Japan, 1959–1960 [52]. *Dashed lines;* Iceland, 1911–1929, Iceland, 1930–1949, Iceland, 1950–1972 [19]. *Broken lines:* Rotterdam and The Hague, the Netherlands, 1972–1974, women < 60 kg, women ≥ 60 kg [50].

dence rates between the Netherlands, where incidence rates are relatively high, and Japan, where incidence rates are low, is related to differences in the weight and height of women in these two areas. Nutrition is thus a subject of considerable interest at present and will be discussed in more detail later in this chapter.

Reproductive Variables

Early age of a woman at the birth of her first child is associated with a decreased risk for breast cancer [30, 46, 73, 97, 110, 146, 169, 184]; further, it appears that full-term pregnancies are necessary for this protective effect [98, 110, 137, 144, 186]. Women who have their first full-term pregnancy before the age of 18 years have about one-third the risk of women whose first full-term pregnancy does not occur until age 35 or older [110]. Most studies indicate that women who give birth to their first child after the age of 30 years are at an even greater risk than those who bear no children at all [110]. One possible explanation of this finding is that the protective effect of early full-term pregnancy is related to prevention of tumor initiation, while the increased risk with giving birth at older ages is related to promotion of cells that are already transformed [108].

Most investigators have found that the greater risk of breast cancer among women of low parity compared with those of high parity is attributable to the tendency of women of high parity to have given birth to their first child at a young age. While in most areas, age of the mother at the first birth does appear to account for the association of parity with breast cancer, there is evidence from studies in Burma [166], Iceland [169], and Sweden [2] that women of very high parity may in fact be protected against breast cancer independently of any association of parity with age at first birth. These recent findings merit further investigation.

The decreased risk for breast cancer among women who are relatively young at the time of the birth of their first child could be brought about by hormonal changes accompanying the pregnancy, or could be related to a factor that causes a delayed first pregnancy and also causes breast cancer. With respect to the latter possibility, it has been hypothesized that anovulatory menstrual cycles, which are associated with persistent exposure to

estrogens without adequate progesterone secretion, and which would be expected to be associated with delayed first birth, could be an important risk factor for breast cancer [64, 157]. However, evidence for an etiologic role of anovulatory menstrual cycles is at present not convincing [64, 97, 165], although more research in this area is warranted. On the other hand, there is some support for the hypothesis that first birth at an early age brings about a permanent change in susceptibility; this will be discussed further in the section on endogenous hormones.

It used to be believed that breast-feeding reduced the risk for breast cancer, but this has not been found in many well-designed studies [73, 82, 97, 111, 112, 163, 166, 184]. Women with a long history of breast-feeding tend to have borne several children, and women who have borne many children tend to have had their first child at an early age. When the woman's age at first birth is taken into account, breast-feeding appears to have no effect on risk for breast cancer.

Several investigators have found that artificial menopause protects against breast cancer [46, 82, 95, 111, 146, 163]. This reduction in risk is probably attributable specifically to removal of the ovaries; and, the earlier the age at oophorectomy, the lower the risk [56, 76]. Women who undergo oophorectomy when they are below the age of 35 have about one-third the risk for breast cancer when compared to women having natural menopause around 45 to 54 years of age. This reduction in risk associated with oophorectomy appears to last for the rest of the woman's life [168].

Most studies show that menarche at an early age [30, 39, 73, 98, 137, 144, 162, 163, 166, 169, 186], and menopause at a late age [30, 39, 73, 98, 137, 163, 166, 168, 184, 186] are associated with an increased risk for breast cancer. It is not known whether a woman's risk is directly affected by the total number of years she has menstrual cycles, or whether age at menarche and age at menopause are important risk factors in their own right, regardless of the number of years of menstrual activity.

Endogenous Hormones

The results of epidemiologic studies clearly suggest that hormones are involved in the etiology of breast cancer. Despite a

large amount of laboratory and epidemiologic research, however, there is still great uncertainty as to which hormones are involved and in what manner they have their effects. The hormones that have been most frequently considered in the etiology of breast cancer are estrogens, progesterone, prolactin, androgens, and thyroid hormones.

Estrogens

Estrogens have long been considered possible mammary carcinogens in women because of (1) the epidemiologic characteristics of breast cancer; (2) evidence that estrogens are carcinogenic in animals, particularly in the tumor promotion stage; and (3) evidence that some tumors respond to the administration of estrogenic or antiestrogenic compounds. The relatively long period of time over which risk factors related to estrogens have their effect suggests that estrogens are involved in tumor initiation, regardless of what role they may have in tumor promotion [107]. It has been noted [44], however, that any simple explanation based on total exposure to estrogens is unlikely since full-term pregnancies at an early age, when estrogen levels are increased, are in fact associated with decreased risk for breast cancer; and, also, there is no decreased risk associated with lactation, when exposure to cyclic estrogens is suppressed.

It was hypothesized by Lemon and co-workers [93], and subsequently in modified form by Cole and MacMahon [44], that the roles of the three main types of estrogens—estrone (E1), estradiol (E2), and estriol (E3)—need to be considered. Cole and MacMahon proposed that the greater the amount of estriol (E3) relative to estrone and estradiol that a women produces during the years immediately after menarche, the lower her lifetime risk of breast cancer. This hypothesis was consistent with the finding from epidemiologic studies that full-term pregnancies protect against breast cancer, since during the third trimester of pregnancy, concentrations of estriol increase greatly relative to estrone and estradiol. This hypothesis was also supported by certain animal experiments which indicated that (1) estrone and estradiol were carcinogenic in certain animals while estriol was, at most, weakly carcinogenic; (2) estriol competed with estradiol for cytoplasmic binding sites; and (3) estriol inhibited the incorporation of estradiol into nuclei of a chemically