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CLINICAL REVIEW

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The epidemiology of breast cancer

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Abstract Breast cancer is the most frequent cancer in women; it attacks about one in ten women during her lifetime, and the incidence has increased almost 100% over the past four decades. The epidemiology of breast cancer (BC) has been intensively assessed in a number of large and often high-quality studies. While many still consider it a disease without known cause, the fact is that BC is also a multifactor disease, with contributing risk factors in the genetic constitution, from foetal exposures and from reproductive parameters. We are able to explain almost the entire increase in the occurrence of this disease primarily by the changes in age at first childbirth, the menarche, number of born children, and the increased frequency of adiposity. Prevention of BC should focus on these reproductive parameters, on alcohol and on physical activity, whereas the prophylactic impact of exogenous hormones, smoking, and lactation is limited.

Keywords Breast cancer · Epidemiology · Aetiology · Hormone therapy · Reproduction

Breast cancer incidence

The incidence rate of breast cancer (BC) increases exponentially with increasing age until about age 50 years (Fig. 1) [1]. Thereafter the curve flatens out and becomes almost horizontal after 70 years. The disease is rare before age 35 years. Figure 1 also indicates the corresponding incidence rates 30 years ago. It appears that the increase is present primarily in the age group 45–75 years. Over the past four decades the incidence has doubled, corresponding to an annual increase of 2–3%. Together with lung cancer, BC is the leading cause of cancer deaths in women. It is generally accepted that the earlier a cancer appears, the higher is the aetiological genetic contribution. Therefore genetic factors and possibly foetal exposures are anticipated to play a major causal role for early BC (before menopause) whereas external exposures and life-style habits may dominate the aetiology of BC after menopause. Several epidemiological findings support that this general view also applies to BC. Although many clinicians are of the opinion that the aetiology of BC is unknown, and we know even less about the reasons for the increase over recent decades, the fact is that we know many quantified risk factors and are able to explain almost the entire increase in incidence over time.

The aim of this contribution is to summarise our knowledge of risk factors for BC and to assess the contributing impact of each of these risk factors for the lifetime risk of the disease.

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Risk factors for breast cancer

Genetic disposition

The proportion of women with at least one first relative (mother, sister or daughter) with BC increases with increasing age. Among women at 50 years about 10% have such a relative. These women have about twice the risk of developing BC as those without BC in close relatives [2]. Among the 10% with a family history of BC a minority have known specific lesions, so-called BRCA1 and BRCA2 mutations, increasing their risk of BC many times. In a majority the genetic constitution is unknown, and our only guide is familial occurrence and the age at which the BC developed. The younger the age, the higher is the risk of being carrier of one of the known genetic mutations. The fact that BC is 200 times more

frequent among women than among men also suggests a combination of genetic and a physiological effects.

Foetal exposures

The risk of BC is associated with women's birth weight [3, 4, 5]. Recent Swedish findings suggest that this association applies only to premenopausal BC, where a birth weight greater than 4 kg implies a relative risk of premenaupausal BC 3.5 times higher than for women with birth weight less than 3 kg [5]. The oestrogen level in a pregnant woman determines the size of the placenta, which in turn is of significance for the growth rate of the foetus. Larger newborns are thus on average exposed to higher levels of oestrogen than smaller babies. The higher risk of BC in large newborns suggests that the primordial breast tissue may be primed by oestrogen in a way which determines the risk of BC decades later. Whether exposure in pregnant women to artificial oestrogens or oestrogen-like substances influences the risk of BC in adulthood is unknown, but not unlikely.

Reproductive parameters

Although foetal exposure to oestrogen is the most important hormonal exposure determining the lifetime risk of BC, the endogenous hormone exposure throughout a woman's fertile period also influences the risk.

Menarche and first delivery

The time between menarche and first delivery is a vulnerable period for breast tissue. The full differentiation of breast glands takes place not until full-term pregnancy and lactation. The undifferentiated glands, as with other immature stem cells, are more sensitive to carcinogens than fully differentiated cells [6, 7]. The longer the time from menarche until first full-term pregnancy, the longer are immature breast glands exposed and the higher is the risk of BC. The lifetime risk increases about 20% for each 5 years that this vulnerable time increases [8].

Number of children born and lactation

The risk of BC decreases with the number of children delivered. For each child born after the first, the risk of BC decreases about 7% [9]. Breast feeding further reduces the risk with about 5% for each year a woman breastfeeds.

Total number of menstruations

In principle during each menstruation cycle the breasts are prepared for a coming pregnancy. Therefore during first half of each cycle breast cells proliferate, followed by cell death and apoptosis if no pregnancy occurs. The number of times that this process occurs is associated with the risk of developing BC [10]. Therefore early menarche or late menopause increases the risk of BC.

External hormones

Use of oral contraceptives (OCs) entails a 7% increase in BC risk as compared with women who have never taken OCs [11]. There is no increased risk of BC after menopause in women who have taken OCs even for many years before menopause [12], and there is no increased risk of death of BC among current or previous users of OCs [13]. The slightly increased risk of premenopausal BC in women who have ever taken OCs has only a limited impact on the lifetime risk of BC, due to the low incidence among young women, where the use of OCs dominates.

Hormone therapy (HT) in or after menopause increases the risk of BC in current users 10–100% depending on the specific regimen and length of use. Combined therapy increases the risk more than oestrogen-only therapy [14, 15, 16, 17]. The randomised study conducted by the Womens Health Initiative [17] found no increase at all in women on oestrogen-only therapy. The risk per year of HT corresponds to the risk per year that the menopause is delayed. Previous use of hormones has no impact on the risk of BC.

If 100 women are treated on combined regimens for five years, they increase their lifetime risk of BC from 9.7% to about 10.2%, or by approx. 0.50% (Fig. 2). Ten years of combined therapy increases the lifetime risk by 1–2 percentage points. If all women stopped HT, about 3% of all BC cases would be prevented (aetiological fraction) [14, 15] (Fig. 1, dotted line). Thus HT has little impact on the overall lifetime risk of BC and even less impact on the risk of BC death, as BC after HT has a better prognosis than BC without preceding HT. The effect of HT on the risk of BC vanishes within 5 years after cessation.

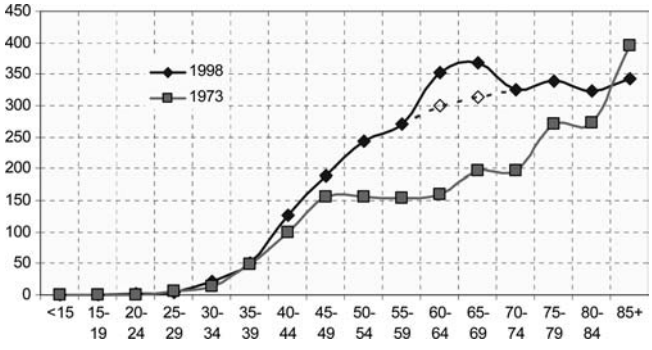

Fig. 1 Age-specific incidence rate of breast cancer in Denmark 1973 and 1998. Incidence per 100,000 women years. *Dotted line* suggests the curve in 1998 if all HT had been withdrawn from market years ago. (From the National Register of Patients and Nordic Cancer Registry)

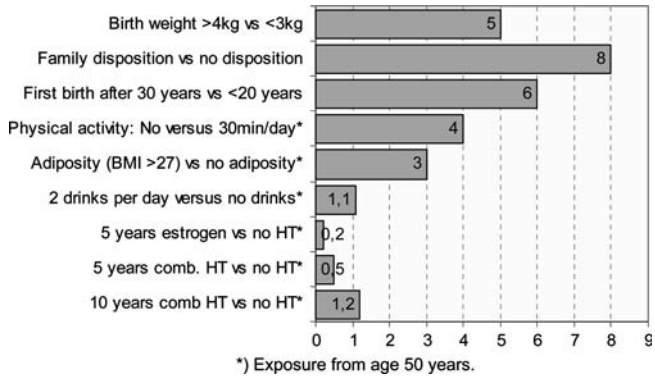

Fig. 2 Consequences of different exposures for lifetime risk of BC. Additional number of BC per 100 women exposed indicated.

Alcohol and adiposity

Daily alcohol consumption increases the risk of BC by 7% per daily drink as long as the use occurs [18]. This increase may be due to decreased liver metabolism of oestrogens in women drinking alcohol. In adipose tissue androstendione is converted to oestrogen. Therefore there is a strong correlation between the amount of adipose tissue and oestrogen levels in postmenopausal women. In premenopausal women the contribution from the adipose tissue is limited compared with the ovaries. Not surprisingly, the risk of BC in postmenopausal women is closely correlated with adiposity, whereas no consistent association is seen in women of fertile age [19]. Even a moderate increase in body mass index (BMI) (>27) increases the risk of BC by 40%.

Physical activity and diet

Several studies have demonstrated a decreased risk of BC with increasing physical activity. Women exercising 30 min per day or more have about half the risk of developing BC as women with a sedentary life-style [20]. High intake of vegetables and fruit in diet has been found to decrease the risk of premenopausal BC by up to 50% compared with women ingesting a low quantity of fibre [21]. A recently published long-term Norwegian follow-up study found a 33% significantly increased risk of postmenopausal BC in women with high-density lipoprotein cholesterol less than 1.2 mmol/l (as seen in women with the metabolic syndrome) compared with women having a level higher than 1.64 mmol/l, after adjusting for differences in BMI [22]. Despite inconsistent results in other studies [23], high intake of vegetables may prevent BC in young women, and low-fat diet may have a probably little preventive impact for postmenopausal BC.

Development in risk factors over time

To what extent are we able to explain the doubled incidence rate of BC demonstrated over the past four decades?

Genetic constitution

The genetic constitution changes but slowly over time and has hardly changed significantly during recent decades. Therefore genetic circumstances probably do not contribute to the increasing incidence of BC observed in recent decades.

Birth weight

Average birth weight has increased during recent decades, and with it the risk of BC. From 1974 until 2001 the average birth weight at term in Denmark increased from 3589 to 3710 g, or by 121 g, corresponding an average increase of 4.5 g per year [24]. Theoretically an increase of 180 g (approx. 40 years) is thought to increase the risk of pre-menopausal BC with 18%, and the lifetime risk with about 4%.

Menarche and age at first birth

The average age at menarche in Denmark has decreased during the past century from 16 to 12 years [25, 26]. It is less certain whether age at menopause has increased [27, 28, 29]. More important is the increasing age at first birth, which in Denmark increased from 23 years in the 1960s to 29 years today. Thus by their earlier menarche and higher age at first birth women on average have increased their BC vulnerable period from about 10 years in 1960s to 17 years today, or by 70%. This increase should theoretically increase the lifetime risk of BC with about 33%.

External hormones

Due to the low frequency of BC in young women, and the small effect of OCs in these age groups, OCs have had little impact on the overall BC morbidity. HT was introduced about 40 years ago, and every second woman takes HT, although often for a short period. HT accounts for 3–4% of the total increase in BC incidence during the past 40 years.

Adiposity

In 1994, 21% of women of reproductive age had an average BMI greater than 25 and 4% a BMI of 30 or more [30]. In 2000 the corresponding figures were 30% and 9%, in fact an epidemic. Such a dramatic increase in BMI will have a profound impact on the risk of postmenopausal BC. In addition to a 50% increase in BC risk among adipose women, a 100% increase in the prevalence of adiposity is expected to increase postmenopausal BC incidence by 14% and the overall incidence with 11%. A continued increase in adiposity over four decades is expected to increase the overall incidence by 40–50%.

Physical activity and diet

Today 13% of women aged 45–55 years have no regular physical activity, and 74% have only moderate physical activity [30]. We have no figures from 40 years ago, and therefore cannot estimate how changes in this aspect of life-style have affected the development in BC incidence. Likewise we have no exact figures on how diet has changed over recent decades. Physical activity and diet, however, probably have had only a minor impact on increase in BC during this period. We do know, however, that alcohol consumption has increased in older women during recent decades. In Denmark daily alcohol intake has increased from 29% in 1987 to 38% in 2000 [30]. The average consumption per person has increased from 1.9 drinks per day in the 1960s to 3.4 drinks per day in the 1990s. This increase in alcohol intake in northern Europe is in contrast to a decrease (although from higher levels) in southern European countries over the past four decades. In Denmark the increase in alcohol in women theoretically has increased the risk of BC with about 10% during this period.

Thus we are able to explain almost the entire increase in BC incidence during the past 40 years. This is in accordance with an analysis by Henderson and Bernstein [31] who were able to explain the majority of the geographical variation from the same exposures. The documented life-style changes are also the areas where attempts to prevent the disease should focus. Much attention has been given to HT. Although these hormones have their share in the increase in BC morbidity (Fig. 1), their impact is limited compared with other life-style changes, many of which we have the possibility of influencing.

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