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Epidemiology of breast cancer in young women

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Introduction

Breast cancer is the most frequent type of cancer among women in the world, affecting up to 12% of all women in Europe and North America [1]. Although less frequent than in older women, breast cancer in younger women is both physically and emotionally devastating. According to the latest National Cancer Institute Surveillance, Epidemiology and End Results database, 11% of breast cancers occur in women younger than 35 years of age (<http://seer.cancer.gov/statfacts/html/breast.html>). Information is limited due to the small patient samples included in studies as well as differences in the definition of “young”, defined by various authors as patients younger than 30, 35, 40, 45, or even 50 years of age.

In women younger than age 30, breast cancer is the leading cause of cancer death for young women in developed countries, constituting 5% to 7% of all cancer deaths in these women [2]. The absolute number of affected women younger than 40 years old is rising, but the incidence of breast cancer in this age group remained stable between 1975 and 2000 in United States [3].

Breast cancer is mainly a postmenopausal disease, with more than three-quarters of tumors being hormone responsive. This hormone dependency interacts with environmental and genetic factors to determine incidence and progression of the disease. Lifestyle and environmental effects are potentially modifiable risk factors and offer the prospect of interventions that might ultimately reduce the global burden of the disease [4].

Breast tumors in young women usually exhibit more aggressive features including larger tumor size, a higher incidence of poorly differentiated tumors, positive lymph nodes, high proliferation rates, higher expression of epidermal growth factor receptor 2 (HER2), and absence of endocrine receptors [5, 6]. Because of this, breast cancer in young patients is often associated with a poorer prognosis [6, 7]. Women younger than 35 years who express estrogen receptors (ER+) tumors have worse outcomes than

older women with ER+ tumors irrespective of treatment. A recent study found that the risk of death rose by 5% for every 1-year reduction in age at diagnosis [8]. This may partly be explained by different patterns of coexpression of key markers at different ages [9]. ER negative (ER-) tumors tend to occur earlier in life, and hence ER+ tumors are more common in older women. The peak ages of onset for these two tumor phenotypes are 50 and 70 years of age, respectively [10].

Clearly, high-risk and low-risk tumors differ with respect to age at onset and hazard patterns, raising the possibility that these are different diseases derived from different pathways. One might speculate that most breast cancers arise from two distinct populations of progenitor cells, with somatic mutations producing tumors with the intermediate risk profiles. What we refer to as “breast cancer” is therefore perhaps a mixture of two different disease processes [11].

Evolution of the incidence of breast cancer

Breast cancer incidence had been either stable or increasing during preceding years. Changes in reproductive factors, in the use of menopausal hormone replacement therapy, in mammographic screening, in environmental exposures and in diet have all been proposed to explain the rising trend. Nowadays, the incidence in many developed countries has started to decrease [12-14].

In the early 1980s, Spain was among the European countries with the lowest incidence of breast cancer, however it experienced a sharp increase over subsequent decades [15]. A variety of factors were associated with this marked rising trend, including a dramatic decline in fertility, the increasing prevalence of obesity, and the higher prevalence of sedentary lifestyle and alcohol consumption in the Spanish population [16]. However, the increase in breast cancer incidence has come to a halt in recent years, and updated data from 2000-2004 showed that the incidence of this disease differed by age group. Among women aged 45–64 years there was an abrupt downturn

in incidence rates in 2001, and among women aged 65 years or older the increasing trend gradually leveled off in 1995 and remained stable thereafter. Among women younger than 45 years, however, breast cancer incidence appears to have increased steadily across this period [16].

To interpret these changes in breast cancer incidence, it is important to consider factors that might influence the observed trends. In most developed countries, where a downturn in breast cancer incidence has been reported, this decline has been associated with a decrease in the use of hormone replacement therapy [12-14, 17]. Hormone replacement therapy use declined after the publication of results from the Women's Health Initiative, the largest randomized trial designed to assess the risks and benefits of hormone replacement therapy that included estrogen plus progestin regimens [18]. The other important explanatory factor to be considered when interpreting changes in breast cancer incidence is screening. The introduction of screening programs perturbs preexisting trends by bringing forward the date of diagnosis, thus resulting in a temporary increase in cancer incidence. Once the program is in place and screening coverage of the target population reaches a plateau, incidence rates tend to decrease because the pool of undiagnosed prevalent cases has reduced. This phenomenon may be explained by early diagnosis of screen-detected tumors that otherwise would have been detected later. Moreover, screening also detects *in situ* carcinomas, which are surgically treated to prevent their progression into invasive tumors. Both factors, diagnostic anticipation and detection and treatment of pre-invasive lesions, could have contributed to the reduced incidence that is observed in the older age groups [19].

The recent increase in breast cancer incidence among Spanish women younger than 45 years calls for specific comment because in many other developed countries, breast cancer incidence among women in this age range has stabilized [12, 14, 17]. A plausible explanation for the continuous increase in breast cancer incidence among

younger women may be the remarkable change in lifestyle that has taken place in Spain during the past two decades. The decline in fertility that has been observed in all European countries was particularly sharp in Spain, where the average number of births per women dropped considerably, and the age at first delivery has increased [16]. On the other hand, the mean age at menarche, a risk factor also associated with the development of breast cancer at younger ages, has decreased at a higher rate in Spain than in other European countries [16, 20].

Risk factors of breast cancer

Tumors with high-risk characteristics are more common among younger women, whereas those with low-risk characteristics are more common in the elderly [1, 7]. Tumors in these two patient populations seem to have different underlying causes and pathobiology. Racial differences have been described. In US, breast cancer incidence is higher in black women than in white women under the age of 50 years, but the reverse is true among older women [21].

The genetic background plays a more important role in early breast cancer. The highest relative risk associated with having a next of kin with breast cancer is found in younger women [22]. High-penetrance genes such as BRCA1 and BRCA2 explain less than 20% of the inherited risk, the rest being accounted for moderate-penetrance and common low-penetrance [23].

Some reproductive and anthropomorphic factors have opposing effects in young women compared to what has been described in postmenopausal women. For example, nulliparity, oral contraceptive use and obesity all decrease the risk of early-onset breast cancers while increase the risk in older women [10].

Nulliparity is a well known risk factor for breast cancer. However, women who defer childbearing beyond 35 years of age also have an increased relative risk compared with nulliparous women. This observation might have relevance to contemporary

reproductive practices. Nowadays, late pregnancies are common increasing the chance of pregnancy-related breast cancer [24]. Furthermore, even though the role of insulin-like growth factor (IGF)-I in breast cancer remains controversial, there is evidence that the adverse effect of IGF-I on the breast is stronger before the maturation of the gland induced by the first full-term pregnancy [25].

The perinatal period seems to be crucial for breast cancer development. Birth characteristic including gestational age, birth weight and birth length are associated with maternal hormone levels. Epidemiological data seem to support the hypothesis that hormonal exposure in uterus increases the risk of breast cancer in adulthood [26]. This exposure has a stronger effect in early breast cancers [26].

Obesity is a established risk factor for breast cancer, but in most studies an inverse relationship has been found between weight or body mass index (BMI) and breast cancer among premenopausal women [27]. The increased incidence of breast cancer in lean young women is found to be strongest amongst the youngest age group (≤ 35 years) [27]. However, a high BMI is significantly associated with an increased risk of inflammatory breast cancer, which is the most lethal form of breast cancer in both premenopausal and postmenopausal women [27]. On the other hand, most large epidemiological studies have found that overweight or obese women are at increased risk of developing postmenopausal breast cancer.

Epidemiological studies consistently show higher risk of breast cancer associated with alcohol consumption. The association is stronger with ER+ tumours, more often observed among postmenopausal women, but a recent meta-analysis confirm that alcohol consumption also increases the incidence of ER- tumours [28].

Physical activity has been consistently associated with lower risk of postmenopausal breast cancer, but its relationship with premenopausal breast cancer is less clear [29]. However, the Nurses' Health Study has recently reported a reduced risk for

premenopausal breast cancer in women engaging in high amounts of physical activity [30].

Conclusions

Breast cancer is a physically and emotionally devastating disease, which can have an even higher impact in young women. Breast tumors in young women are characterized by a decreased expression of endocrine receptors, and are often associated with a poorer prognosis. Breast cancer incidence in Spanish young women appears to be increasing, although in many other developed countries, the incidence has stabilized. This may be explained by changes in lifestyle, decline in fertility, and decreased mean age at menarche. Genetic predisposition is a stronger risk factor in early breast cancer and the same is true for higher in utero exposure to estrogens. Obesity is a protective factor for women younger than 50 years, but increases the risk of developing breast cancer thereafter. Nulliparity is a well known risk factor for breast cancer. However, women who defer childbearing beyond 35 years of age also have an increased relative risk compared with nulliparous women. Finally, physical activity has a protective effect on breast cancer development.

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