Editorial

The burden of breast cancer from China to Italy

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Breast cancer is the second most common cancer in the world and the most frequent cancer among women, with an estimated 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers) (1). In Europe the estimated age-adjusted annual incidence of breast cancer in 2012 was 94.2/100 thousand and the mortality 23.1/100 thousand (2). In USA, according to the SEER database [2006-2010], the age-adjusted annual incidence of breast cancer was 123.8/100 thousand and the mortality 22.6/100 thousand (3). The median age at breast cancer diagnosis is 61 years: about 10% of breast cancers occur among women aged younger than 50 years, while 65% occur among women aged 65 years or older (3). Overall, 60% of breast cancers are diagnosed at a localized stage, 32% at a regional stage and 5% at an advanced stage. The 5-year relative survival rate for women diagnosed with localized breast cancer is 98.6%; survival declines to 84.4% for regional stage and 24.3% for distant stage (3). In western countries, due to both early detection through screening programs and the improvement in the available treatment strategies, the percentage of women surviving at least 5 years after diagnosis and treatment has shifted from 74.8% in the early 1970s to 90.3% in the late 1990s (3).

In Italy, it has been estimated that approximately 48,000 new cases of breast cancer has been diagnosed in 2013 (4). Excluding skin cancers, breast cancer is the most common cancer diagnosed in women: a total of 41% are diagnosed in the age group 0-49 years, 36% in patients aged 50-69 years and 21% in women older than 70 years (2,4,5). Breast cancer incidence and prevalence present a marked north-to-south gradient: the incidence rates are respectively 124.9, 100.3 and 95.6 per 100 thousand in the northern, central and southern areas (5). Regarding breast cancer prevalence, the proportion of prevalent cases in the northern area is remarkably higher (2,055-2,331 per 100 thousand) than in the central area (1,795 per 100 thousand) and about twice than in the southern area (1,151 per 100 thousand). In Italy, breast cancer mortality increased until the late 1980s reaching its maximum value at approximately 27 per 100 thousand, and started to decline thereafter (approximately –1.6%/year) (2). The mortality rate started to decline from the late 1980s in the northern central regions and from the mid-1990s in the southern regions. The 5-year relative survival increased from 78% in 1990-1992 to 87% in 2005-2007 (6,7); age standardized mortality rates are lower in the central area (20.6 per 100 thousand) than in the northern (24.7 per 100 thousand) and southern (25.2 per 100 thousand) areas (4).

Breast cancer is a major burden also for Chinese women: Zeng and colleagues recently described the epidemiology of breast cancer in China in 2010, reporting breast cancer statistics by age and geographical area (8). Authors estimated the status of female breast cancer based on existing population-based cancer registries' data available in 2010; these registries covered approximately 12.96% of the overall female population in China. The estimated number of female breast cancer cases was about 208 thousand; the overall crude incidence rate was 32.43 per 100 thousand, accounting for 16.2% of all cancer cases in Chinese women (first cause of cancer diagnosis). The rates standardized by World population and by China population were 24.20 per 100 thousand and 25.89 per 100 thousand respectively. The estimated number of female breast cancer death was about 55.5 thousand with an overall crude mortality rate of 8.65 per 100 thousand, accounting for 7.90% of all cancer deaths (fifth cause of cancer deaths in Chinese women). After age standardization by China population and World population, the standardized rates were 6.56 per 100 thousand and

6.36 per 100 thousand respectively. After stratification by area, the incidence of breast cancer was higher in urban area than in rural area. The age-specific incidence rate resulted relatively low before 25 years old, but dramatically increased after then; the trend of age-specific incidence in urban and rural area were similar as the overall incidence. The mortality rates by geographical area had a similar pattern as the incidence rates, increasing with age. In conclusion, breast cancer is still a major health burden in China, especially for women living in urban area; authors suggested that prevention strategies (for example weight control and breastfeeding promotion), high quality screening and diagnosis might help to reduce breast cancer mortality and to control the disease (8).

In the interpretation of the epidemiology of breast cancer, multiple risk factors, the implementation of breast cancer screening and the improvement in cancer therapy should be taken into account. In recent years, the substantial progresses in the management of stage I-III breast cancer led to a better prognosis for breast cancer patients. However, many women every year in the world die for disease; strategies for primary and secondary prevention should be implemented to reduce the burden of breast cancer.

Several risk factors are associated with breast cancer risk; they are divided into two categories: the non-modifiable and the potentially modifiable risk factors (9). The purpose of primary prevention is to reduce the incidence of cancer, keeping under control the modifiable risk factors, such as: life-style (obesity, alcohol consumption, diet rich in carbohydrates and saturated fats, physical inactivity), some reproductive factors (nulliparity, old age at first pregnancy, no breastfeeding) and use of hormone replacement therapy.

Petracci and colleagues identified three modifiable risk factors in Italian women (physical activity, alcohol consumption and body mass index) on which to base prevention strategies (9). Authors showed that a regular daily physical activity combined with a balanced mediterranean diet can reduce the risk of postmenopausal breast cancer women of approximately 1.6% in 20 years, rising to 3.2% in women with a positive family history and 4.1% in women at high risk (9).

Not only the improvements in lifestyle but also a pharmacological prophylactic treatment (chemoprevention) seems to have an important role in reducing the incidence of breast cancer, especially for women at high risk (defined as a 10-year risk of breast cancer of 5% or more). Recently, Cuzick and colleagues performed an individual participant data meta-analysis to better clarify the role of selective estrogen receptor modulators (SERMs) in the primary prevention of breast cancer (10). Authors showed an overall 38% reduction in breast cancer incidence with the use of tamoxifen or other SERMs [hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.56-0.69]; the benefit was shown only for estrogen receptor positive breast cancer (HR 0.49, 95% CI: 0.42-0.57) and not for estrogen receptor negative tumours (HR 1.14, 95% CI: 0.90-1.45) (10). Two recently published randomized trials assessed the role of aromatase inhibitors (AIs) for breast cancer prevention in high risk postmenopausal women. In the MAP.3 trial, exemestane significantly reduced the incidence of all breast cancer by 53% (HR 0.47, 95% CI: 0.27-0.79) and invasive breast cancer by 65% (HR 0.35, 95% CI: 0.18-0.70) after a median follow-up of 3 years (11). The IBIS-II trial, after a median follow-up of 5.0 years, showed a reduction in the risk of breast cancer and ductal carcinoma in situ by more than 50% with the use of anastrozole (HR 0.47, 95% CI: 0.32-0.68) (12). Both trials recorded no significant differences between groups for cardiovascular events; many side-effects associated with estrogen deprivation were poorly more frequent in the treatment group than in the placebo group, indicating that most of these symptoms are not drug related. Based on this data, the American Society of Clinical Oncology (ASCO) guidelines recommend the use of chemoprevention in women at increased risk of breast cancer, defined as individuals with a 5-year projected absolute risk of breast cancer ≥1.66% (based on the National Cancer Institute Breast Cancer Risk Assessment Tool or an equivalent measure) or women diagnosed with lobular carcinoma in situ. Specifically, in women at increased risk of breast cancer older than 35 years, tamoxifen (20 mg per day for 5 years) should be discussed as an option to reduce the risk of estrogen receptor-positive breast cancer; in postmenopausal women, raloxifene (60 mg per day for 5 years) and exemestane (25 mg per day for 5 years) should also be discussed as options (13). In Italy the use of SERMs or AIs for breast cancer prevention is only possible so far in clinical trials or as "off-label" drugs.

The goal of secondary prevention is to detect cancer at an early stage; among the current available screening methods, mammography seems to be the most sensitive and specific. Mammography screening has been shown to have the greatest effect on breast cancer mortality reduction in the age group of 50-69 years and it is recommended by the European Society for Medical Oncology (ESMO) guidelines in this age group (14). In contrast, the role of

mammography screening in women aged 40-49 years is debated and seems to be associated with lower efficacy and cost-effectiveness (14).

The increase in survival among breast cancer patients observed in Italy since 1990, is consistent with the improvement in local and systemic treatment and, above all, with the diffusion of screening programs. Organized screening programs started at the beginning of the 1990s and contributed to an increase in breast cancer detected at an early stage and with a better prognosis (15). They were first restricted to certain northern areas, including less than 5% of the target population (16). From the second half of the 1990s different screening programs were activated in central Italy coming to involve 15% of the women between 50 and 69 years (16). In Italy, breast cancer screening is based on bilateral mammography and is recommended every two years in women aged 50-69 years. In women aged 40-49 years, mammography should be performed according to individual risk factors (for example family history and the density of breast tissue); recently, according to the National Plan for Prevention 2005-2007 mammographic screening should be extended in women with 45-49 years of age, performed every 12-18 months. For women older than 70 years, there is no evidence of the efficacy of mammography screening and therefore is not recommended. Since 2007, the organized screening activity is present in all Italian regions but with great differences in the adherence among the different geographical areas. Data analysis from 2000-2010 shows that crude attendance rate reached an acceptable value of 50%, but with a higher level of participation in northern and central Italy as compared to southern Italy where attendance rates are still inadequate and do not reach the acceptable standard (17). The rise in breast cancer incidence showed in Italy during the 1990s might be explained by the effect of screening, especially in the northern-central area, while the stabilization of incidence rates estimated for many northern-central regions from the late 1990s could be explained by the exhaustion of the initial screening effect (18). Such a situation cannot yet be hypothesized for southern regions because of the late initiation and the low adherence to the screening program.

The improvements in breast cancer care, including the more widespread use of adjuvant systemic therapies, and the progress in radiotherapy and surgery, are likely to be the major determinants of the mortality reduction in Italy in the late 1980s and early 1990s, before the screening program could have produced its effect. The decrease observed in mortality for the northern-central regions from the late 1980s and for Italy as a whole from the early 1990s may be related to both improved treatment and early detection diffusion. The delay in the mortality decline in the southern regions may be explained with the limited coverage areas of screening programs, the lesser attendance in screening programs with more late stage diagnosis of breast cancer and the disparities in cancer care with respect to northern-central regions (18,19). The current gap in the breast cancer prevalence between northern-central and southern regions is mainly attributable to the pronounced differences in past levels, which were much higher in the northern and central areas than in the south (20).

In conclusion, breast cancer is still a major global health problem. The geographical variation in female breast cancer burden can be partially explained by differences in the risk factors and in the distribution of screening among different countries and among different regions within the same country. Lifestyle interventions such as weight reduction, low-fat diet, reduced alcohol intake and exercise should be included in programs to prevent breast cancer, and for women at high risk of breast cancer, where available, chemoprevention strategies could also be proposed. Moreover, a more widespread screening activity would help to close the gap between countries and regions within the same country. A continuous monitoring of regional epidemiological indicators for breast cancer is very important to evaluate the effect of different health measures taken to control breast cancer.

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