Risk factors for breast cancer in China: similarities and differences with western populations

Federica Turati[1,2], Carlo La Vecchia[1,2]

[1]Dipartimento di Epidemiologia, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
[2]Dipartimento di Medicina del Lavoro, Università degli Studi di Milano, Milan, Italy

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Corresponding author:
Prof. Carlo La Vecchia
Dipartimento
di Epidemiologia
Istituto di Ricerche
Farmacologiche
"Mario Negri"
Via La Masa 19
20156 Milan, Italy
Phone: +39 0239014527
Fax: +39 0233200231
E-mail:
carlo.lavecchia@marionegri.it

The study by Xu *et al*., reported in this issue of the *Archives of Medical Science*, is a large original study on breast cancer risk factors in China, a country with low breast cancer incidence [1, 2]. The study shows results from the project of breast cancer prediction (BCPC) in China, aiming to screen breast cancer risk factors among Chinese women and predict individual risk of breast cancer through established risk factors. It is a multicentric hospital-based case-control study, carried out in 14 hospitals in 8 provinces of China, and, from January to July 2008, recruited 416 women aged 30 to 65 years with incident breast cancer and 1156 healthy women.

We are not commenting upon stress anticipation, which goes beyond our area of expertise. Apart from this, results from the BCPC study are only partly in agreement with those from studies from Western Countries, thus suggesting a somewhat different pattern of risk factors for the Chinese population.

In particular, the study confirms the role of history of benign breast disease biopsy in breast cancer [2], estimating an adjusted odds ratio (OR) of 1.68 (95% confidence interval – CI – 1.19-2.38).

Moreover, in agreement with most literature on breast cancer and family history of breast cancer [3-6], the BCPC study found a positive, though not significant, association between having a first degree-relative affected by breast cancer and the risk of breast cancer (OR = 1.66, 95% CI: 0.77-3.59).

Reproductive and hormonal factors play a central role in the etiology of breast cancer [7]. Earlier menarche and later menopause are well established risk factors for the development of breast cancer [8-10], being responsible for a prolonged lifetime exposure to endogenous hormones [11]. The risk of breast cancer decreases by about 5% with each 1-year delay in menarche [11-14] and, on average, the risk increases by about 2.7% for each year menopause is delayed [13]. The positive association between age at menarche and breast cancer risk found by Xu *et al*., with an OR of 1.41 (95% CI: 1.07-1.87) for women with menarche at age 14 years or more, is inconsistent with the overall evidence. The increased risk associated to menopause was also controversial, given the similar mean age at menopause among cases and controls (i.e., 48.89 vs. 49.33 years, respectively). Likewise, the Japan Collaborative Cohort Study, prospectively examining more than 38,000 women in a traditionally low-risk population as Japan, found no association between breast cancer and age at menarche and at

menopause [8]. Still, accurate adjustment for age and socioeconomic factors is required for any inference on these factors.

In the BCPC study, parous women represent almost the totality of cases and controls, and parity tended to be uniformly low. Likewise, the apparent uniformity of age at first birth may explain the limited association with this well recognized risk factor [15-17]. No meaningful differences emerged between women with and without breast cancer in terms of number of live births and age at first live birth. Conversely, epidemiological literature consistently found that a younger age at first full-term pregnancy is associated to a lower lifetime risk of breast cancer, and that a higher number of births is related to a lower risk [2].

A protective effect of lactation on breast cancer has been reported by several studies [3], including the pooled analysis by the Endogenous Hormones and Breast Cancer Collaborative Group, which found that lifetime duration of breastfeeding was associated to a significant reduction in breast cancer risk among parous women, with a relative risk (RR) decreasing by 4.3% for every 12 months of breastfeeding [18]. Data in the BCPC study are however inadequate to materially contribute to the issue.

There is definite evidence that abortions are unrelated to excess risk of breast cancer [19, 20]. A recent pooled analysis of 53 studies carried out in 16 countries found no association between spontaneous abortion and breast cancer, but a moderate protection for induced abortion [20]. However, when the analysis was restricted to studies with a prospective design, the risk of breast cancer did not differ significantly according to the number or timing of either type of abortion. The null association reported by Xu *et al*. is therefore in line with the most recent literature.

Evidence on the association between oral contraceptive (OC) use and breast cancer indicates a modest increased risk, however restricted to current or recent use, or the absence of any association after 5 years or more since stopping [21-24]. Moreover, consistent findings from observational studies and randomized trials showed an increased breast cancer risk among women using combined estrogen–progestogen therapy in menopause [25-27]. The risk increases with increasing duration of use but decreases after cessation, leveling off after 5 years since stopping postmenopausal hormone use [25]. Crude results by Xu *et al*. were apparently in line with the overall evidence, with about 5.6% of cases and 3.9% of controls reporting OC use, and about 5.4% of cases and 2.5% of controls reporting hormone replacement therapy use; however the data were inadequate to perform detailed analyses of such relations by duration and timing of exposure, including time since stopping, which is the key factor for these variables.

The BCPC study found an excess risk of breast cancer among overweight/obese subjects. After adjustment for selected risk factors, including menopausal status, the OR for body mass index (BMI) $\geq$ 24 kg/m^2 as compared to BMI < 24 kg/m^2 was 4.07 (95% CI: 2.98-5.55). It is well known that the relation between BMI and breast cancer depends on menopausal status, with an inverse association among premenopausal women [3, 28-30], likely due to a more frequent anovulation in obese [31-33], and a moderate direct association among postmenopausal women [34]. Body mass index increases postmenopausal breast cancer risk mainly through elevated levels of circulating estrogens, particularly estradiol, in overweight women [34]. After menopause, adipose tissue is the major source of estrogen; moreover, overweight women have low levels of sex-hormone-binding globulin, resulting in a higher level of bio-available estrogens [34, 35]. Xu *et al*. investigated the association between BMI and breast cancer with no distinction between pre and postmenopausal status; thus the estimated OR for overweight women may underestimate the real association in postmenopausal women. Nonetheless, Xu *et al*. found an increased OR of about 4-fold for BMI $\geq$ 24 kg/m^2, somewhat higher than expected on the basis of accumulated evidence on such relation in postmenopausal women [2, 3, 34-36]. In a pooled analysis of three Italian case-control studies, including a total of 3108 postmenopausal breast cancer patients and 2604 controls, ORs for successive BMI quintiles ranged from 1.2 to 1.4, as compared to the lowest quintile, and the association was stronger among elderly women [36]. A pooled analysis from the Endogenous Hormones and Breast Cancer Collaborative Group, including data from eight prospective studies of postmenopausal women, for a total of 624 case subjects and 1669 control subjects, found ORs of 1.17, 1.50, 1.78, and 1.50 for successive categories of BMI, as compared to BMI < 22.5 kg/m^2 [35]. It has been suggested that the relation between weight and risk of breast cancer in low risk areas, as China, may be different from that observed in Western countries, with a lack of association for premenopausal breast cancer and a stronger association for postmenopausal breast cancer [2, 37]. Results from the BCPC study are in agreement with this hypothesis, and suggest a substantial excess risk for overweight women in a population with a low prevalence of overweight and among relatively young women (mean age was around 46 years for both cases and controls). Not surprisingly, therefore, the RR appears to be particularly elevated in overweight women, though the absolute risk and the population attributable risk [38] are not necessarily greater in Chinese than in Western populations.

Alcohol intake is the most consistent dietary factor related to breast cancer [39-41]. Heavy alcohol intake, defined as the consumption of 3 or more drinks/day, was found to be associated with an increased risk of breast cancer by 40-50% [40]. For light drinking (≤ 1 drink/day), a significant increase risk of the order of 4% has been estimated from a meta-analysis updated to November 2011 and based on 113 studies [40]. From individual data from 53 epidemiological studies of breast cancer, the Collaborative Group on Hormonal Factors in Breast Cancer found that, compared with non drinker women, the RR of breast cancer was 1.32 (95% CI: 1.19-1.45) for women drinking 35-44 g of alcohol/day, and 1.46 (95% CI: 1.33-1.61) for those drinking ≥ 45 g/day, with a RR of breast cancer increasing by about 7% for each additional 10 g/day of alcohol intake [41]. Conversely, a recent case-control study conducted in China on more than 1000 incident breast cancer cases found an inverse association with low-to-moderate alcohol intake [42]. Xu *et al*. reported a null association between alcohol drinking and breast cancer risk, although the low prevalence of women who reported to drink alcohol in the BCPC study (about 9% of both cases and controls) do not allow to explore the relation in detail.

The possible effect of smoking on breast cancer risk has been investigated in a large number of studies [41]. Globally, data provided evidence that cigarette smoking is not associated with an appreciably increased breast cancer risk, as also emerged in the BCPC study.

One of the limits of the study by Xu and *et al*. is the lack of information on hormone receptor status. Recent epidemiological evidence suggests that the etiology of hormone receptor defined breast cancers may be heterogeneous [43-45]. In a recent systematic review collecting information on 31 studies, delayed childbearing and nulliparity were associated with increased risk of developing estrogen receptor (ER)+ breast cancers but not ER– breast cancers, whereas early age at menarche and postmenopausal obesity were more consistently associated with increased risk of hormone receptor-positive than hormone receptor-negative tumors [43]. In 2006, a meta-analysis focused on reproductive factors found that the protective effect of parity and early age at first birth was confined to ER+/progesterone receptor (PR)+ cancers, while that of late age at menarche was significant in both subtypes of breast cancer, although stronger for ER+/PR+ than ER–/PR– cancers [44]. On the other hand, breastfeeding [43, 44], alcohol, smoking, family history of breast cancer, and premenopausal obesity [43] were similarly associated with both hormone receptor-defined breast cancers. Although it has been suggested that ER/PR status varies among racial groups and results from these reviews [43, 44] were derived from studies conducted predominantly on Western populations, comparable findings were obtained by the Shanghai Breast Cancer Study [45]. In studies focused on breast cancer as a single entity, as that by Xu *et al*., some associations restricted to a breast cancer subtype could be diluted or masked.

Still, the BCPC study is an important original contribution towards our quantification of breast cancer risk factors.

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