Chapter 6

Discussion

The present study examined the association between reproductive and anthropometric factors as well as physically strenuous household activities and breast cancer risk by menopausal status. In India, there are a few studies reported the association between reproductive factors and breast cancer risk (Rao et al., 1994; Jussawalla et al., 1981), however, there are no studies showing the association between anthropometric factors as well as level of physical activity and breast cancer are reported. The present study is the largest case-control study in India showing the association between the above factors and breast cancer risk.

Findings of the present study suggested that reproductive factors play a role in the development of breast cancer not only in Western populations but also in low-risk populations as well. Previous studies in Asian countries have reported that reproductive factors such as early age at menarche and late age at menopause are risk factors for breast cancer (Hirose et al., 1995; Nagata et al., 1995; Talamini et al. 1996; Goodman et al., 1997; Gao et al., 2000; McPherson et al., 2000; Tamakoshi et al., 2005; Yavari et al., 2005; Naieni et al., 2007). In the present study also, it is observed that early age at menarche, and late age at menopause were at elevated risk of breast cancer among post-menopausal women. However, in the present study, early age at menarche was not observed as a significant factor after adjusted for potential confounder among pre-menopausal women.

In the present study, it is observed that increased parity among breastfed women is inversely associated with breast cancer after adjusted for potential confounders. These
information supports the evidence of previous studies that parous women have a lower risk than nulliparous women (Kelsey et al., 1993; Wohlfahet et al., 1999; Tamakoshi et al., 2005; Colditz et al., 2006, Nichols et al., 2006).

In most of the studies, the comparison group is ‘never breastfed’ parous women or a combination of unmarried, nulliparous and never breastfed parous women. Compared to ‘never’ breastfed women were at elevated risk of breast cancer as compared to breastfed women. In the present study, nulliparous women were excluded from the analysis related to history of breast-feeding. This case-control study revealed 38-52% a risk reduction of breast cancer among pre-menopausal women who breastfed for more than five years compared to those breast-fed for less than or equal to one year in their lifetime. The present study observed an inverse dose-response relationship with duration of breast-feeding in pre-menopausal women is in accordance with results from several epidemiologic studies (McTiernan and Thomas 1986; Yoo et al., 1992; Thomas et al., 1993; Brinton et al., 1995; Romieu et al., 1996; Gilliland et al., 1998; Tryggvadottir et al., 2001). The protective effect of 61% reduction in breast cancer risk is apparent only after prolonged period of breast-feeding (OR: 0.39; 95% CI: 0.19-0.80 for breastfeeding >7 years) and is limited to pre-menopausal women only.

Breast-feeding for long duration was common in Kerala. The prevalence of prolonged breast-feeding is low in Western countries since majority of women have two or fewer live births, and the average duration of breastfeeding per child is 4 months (Brinton et al., 1995). Since the protective effect of breast-feeding is observed only with long duration, the studies conducted in Western countries where breastfeeding duration is generally shorter may have limited power to detect significant protective effect.

In the present study, the breast cancer risk was inversely associated with multiparty (for parity >3) in both pre-menopausal as well as postmenopausal women in
the univariate analysis and produced quite similar results of previous studies (Nichols et al., 2006; Tamakoshi et al., 2005; Wohlfahet et al., 1999).

The recall of information on various reproductive factors is more difficult for older women compared to younger ones. It can be assumed that women recalled accurately the fact of having breastfed or not. However there may be some information bias with regard to the exact duration of breast-feeding for each child because the women would have breastfed decades before the start of this study. We assumed this is non-differential and would underestimate the association between breast cancer risk and lifetime duration of breastfeeding in postmenopausal women.

The biological mechanism behind the elevation in risk for early age at menarche in life or late menopause is possibly due to an increased number of ovulatory cycles and/or exposure to estrogen and other breast tissue proliferative hormones (Henderson et al., 1996). The biological mechanisms underlying the protective effect seen with breastfeeding, particularly to pre-menopausal women, is unknown; however the following mechanisms have been postulated.

The proportion of differentiated cells in the breast is increased by pregnancy as well as by lactation. Since this occurs before exposure to carcinogen, breasts are protected from malignant transformation (Russo et al., 1982); the prolonged period of lactation is generally associated with a longer period of lactational amenorrhoea and thus exposure to total estrogen, which has been related to proliferative and carcinogenic effects, has been reduced (Henderson et al., 1985); breast fluid estrogen levels, independent of serum estrogen levels, was lower in breast-feeding pre-menopausal women compared to never lactated (parous or nulliparous) and took several years after the last breast-feeding to reach levels found in nulliparous women (Petrakis et al., 1987).
The present study also assessed the difference in incidence of breast cancer according to menopausal status. Several anthropometric factors were associated with breast cancer risk in both pre-menopausal and post-menopausal women. Few epidemiological studies have addressed the association of anthropometric factors and the risk of developing breast cancer in India. Our findings of an increased breast cancer risk associated with augmented anthropometric factors in post-menopausal women are in accordance with results from previous studies (Carmichael and Bates 2004; Adderley-Kelly and Williams-Stephans 2003; Vainio and Bianchini 2002). In the present study we observed an increased breast cancer risk associated with augmented anthropometric factors and larger body size at 20-years of life in pre-menopausal women also. There are relatively few studies on pre-menopausal women and the overall evidence is inconsistent. The incidence of breast cancer among pre-menopausal women is low in high-resource countries [e.g., the proportion of breast cancer cases under the age of 50 years is around 20% in the US in contrast to around 50% in Trivandrum (Parkin et al., 2002)] and this might be the reason for the inconsistent results among pre-menopausal women.

Several hypothesized biologic mechanisms exist to explain how anthropometric factors influence breast cancer risk. Obesity may increase levels of circulating endogenous sex hormones, insulin and insulin-like growth factors that all, in turn, increase breast cancer risk (Vainio et al, 2002). Our study results among pre-menopausal women are in agreement with some of the previous studies (Dettenborn et al., 2008; Noisadah et al., 2005) for obese or overweight women. However the association is less consistent with previous studies among post-menopausal women (Iwasaki et al., 2007; Palmer et al., 2007; Naieni et al., 2007; Li et al., 2006; Boyd et al., 2006; Rinaldi et al., 2006; Chow et al., 2005; Tehard et al., 2006; Key et al., 2003; Lahmann et al., 2003), although we observed non-significant elevated association. Compared to previous epidemiological studies, our study reported positive association between increased breast cancer risk for increased waist circumference among post-menopausal women (Li et al.,
Larger body size at 20 years of age also produced similar results as compared to previous literature irrespective of menopausal status (Li et al., 2006; Lahmann et al., 2003).

The lack of an association between increased WHR and risk of breast cancer is not fully consistent with previous evidence (Harvie et al., 2003; Connolly et al., 2002). The reason of the discrepancy can be measurement error in our study as well as a different effect of fat distribution on breast cancer risk in India, particularly in Kerala, as compared to high-resource countries.

Weight gain during adulthood has been identified as a risk factor for breast cancer in most studies in which it was investigated particularly for post-menopausal women (Han et al., 2006; Trentham-Dietz et al., 2000). Weight gain among post-menopausal and height gain among pre-menopausal during adulthood were considered ‘probable’ cause of breast cancer by the WCRF (WCRF 2007). In the present study, it was observed that the increased body size during adulthood increased the breast cancer risk irrespective of menopausal status.

Physical activity has also been hypothesized to protect against the development of breast cancer. Few epidemiological studies have been conducted to determine the association of physical activities with the risk of developing breast cancer in India. However, a large number of epidemiological studies have now examined this association in other populations and convincing evidence exists that physical activity reduces the breast cancer risk. The evidence is stronger for post-menopausal women than pre-menopausal women (Monninkhof et al., 2007; Friedenreich 2004). The present study finding of inverse association between breast cancer risk and physical activity is in accordance with the above systematic review from several case-control and cohort
studies on pre- and post-menopausal women. A strong inverse association with dose-response relationship was observed between physical activity and breast cancer risk in post-menopausal women. Women who spent more time on physically strenuous household activities such as cleaning the house, carrying water, and washing clothes (without machine) showed reduced risks of breast cancer. Even though monotonic decreased risks were not observed with increased level of household activities, a significant inverse association was observed in pre-menopausal women also.

Several biologically plausible mechanisms have been proposed in the association between physical activity and risk of breast cancer. Increased physical activity might decrease estrogen and progesterone levels, enhanced natural immunity, and reduction in levels of insulin and other growth factors, prevent women from weight gain and development of obesity, particularly after menopause (Vainio and Bianchini 2002; Ulrich et al., 1998).

In the present study, the proportion of time spent on watching television (an indirect measurement of lack of physical activity) was non-significant among pre- and post-menopausal women. Further no increased risk was observed for women who spent more time for watching television, who spent 2-3 hours/day compared to nil or less than one hour/day irrespective of menopausal status. This is not fully supporting the hypothesis that increased sedentary activities increases the risk for development of breast cancer. However, these women might be doing mainly other types of sedentary activities like sleeping, reading etc. and information on these activities were not collected in the present study.

An inverse association between employment in physically demanding occupations and breast cancer risk compared to sedentary ones was reported in some studies (Kruk and Aboul-Enein 2003; Yang et al., 2003). However in the present study, a non-
significant reduced risk was found for occupations such as farmer/agricultural workers in post-menopausal women and industrial workers in pre- and post-menopausal women after adjusted for potential confounders.

In the present study, the degree of confounding was evaluated by observing the crude and adjusted risk estimates. Several models based on the potential confounding factors were constructed. In the risk estimation if the degree of confounding <10%, the potential confounders were not included as the confounding variables only ‘overfit’ the data. Strong positive confounding effect was observed for variables such as age at first pregnancy, and age at first childbirth and for variables such as age at marriage and body size at 20 years, negative confounding effect was observed. Assessment of degree of confounding provided the information for inclusion or exclusion of potential confounders in the risk estimation. These findings underlie the importance of adequate control for confounding.

The analysis of interaction between risk factors also helped to avoid the ‘overfit’ of data. The role of interaction between BMI and physical activity as well as parity among breastfed women and lifetime breastfed duration among parous women were also assessed and found non-significant associations. However less breastfed duration is one of the few known risk factors for breast cancer which is modifiable; hence advocating breast-feeding by appropriately educating women will benefit not only child health but may reduce breast cancer burden as well.

The attributable risk is estimated for prevention of a disease if one eliminates the exposure. The calculation of attributable risk based on hospital-based case-control study is limited, as the exposure prevalence is unknown. In the present study attributable risk is calculated assuming that the controls are representative of the general population. The
exposure prevalence was obtained based on the proportion among controls. In the present study, it was observed that a total of 50% of expected breast cancer cases among pre-menopausal women can be prevented if women have normal body mass index, early age at pregnancy, and increased physical activity. Similarly a total of 47% of expected breast cancer cases among post-menopausal women can be prevented if women have normal waist and hip sizes, normal body size at early years and increased physical activity. This information leads to the importance of breast cancer primary prevention.

As with any case-control study, it is possible that the case participants may have recalled certain exposures differently than control participants, especially for exposures widely thought to be associated with breast cancer self-reported and may be subject to recall bias. However, the relationships between various reproductive factors, body sizes at different ages and levels of physical activity and breast cancer risk were largely unknown to the study subjects. It is therefore unlikely that the case participants would have over reported their body size or underestimated their physical activity levels or reproductive factors relative to the control participants because of prior knowledge of an association of either of these factors with breast cancer risk. However, measurement error (non-differential misclassification), leading to loss of power and underestimate of OR is a plausible source of bias.

Although the present study has certain limitations inherent to case-control studies, its advantages include a large sample size (it is largest case-control study of breast cancer to date conducted in India), and there by a large heterogeneity of distribution of exposures due to all these factors with more than 90% participation rates in both cases and controls.