CHAPTER 2

REVIEW OF LITERATURE
Chapter 2

Review of literature

This chapter provides the pattern of breast cancer incidence and mortality rates worldwide. Incidence rates of this disease from all the available cancer registries in India are also provided. The subsequent session is a detailed review of literature on the role of various breast cancer risk factors according to the menopausal status. Risk estimates according to the factors such as genetic and familial aspects, exogenous estrogen exposure, reproductive factors such as early menarche, late menopause, nulliparity, late age at first child birth, less duration of breast feeding; anthropometric factors such as increased body mass index and waist-to-hip ratio; physical inactivity; certain diet such as increased use of dairy products and meat and reduced use of fruits and vegetables and other exposures such as pesticide use and ionizing radiation are provided.

2.1. Magnitude of breast cancer

2.1.1 Global scenario

Breast cancer is most frequent cancer of women with an estimated 1.15 million new cases in 2002, ranking second overall when both genders are considered together. The disease is more common in developed countries. However it is a major public health problem in developing countries also. Incidence rates (the number of new cases of breast cancer that occurs during a specific period of time in a population at risk) of this disease vary widely around the world. More than half of the cases occurred in developed countries, that is, about 361,000 cases in Europe and 230,000 cases in North America, which accounts for 27.3% and 31.3% of all cancers among women respectively in the year 2002 (Globocan 2002).
For comparison of incidence and mortality rates among various countries, the age-standardized rates (the incidence or mortality rate which is adjusted to the five-year age distribution of the world standard population is called the age-standardized rate) are used.

The age-standardized incidence and mortality rates per 100,000 women for breast cancer across the world are provided in Table 2.1. Incidence rates are high in most of the developed nations with highest age-standardized incidence rate of 99.4 per 100,000 women was reported in Northern America. The incidence is modest in Eastern Europe, South America, Southern Africa and Western Asia, but it is still the most common cancer among women in these geographic regions. It ranks first among all female cancers in Asian and African populations, although the incidence rates are found to be low (<30 per 100,000 women). The lowest incidence is observed in middle Africa with an age-standardized incidence rate of 16.5 per 100,000 women (Parkin et al., 2005) (Table 2.1).

Mortality rates can serve as a measure of disease severity and is defined as the number of deaths due to specific disease of interest in a population, scaled to the size of that population per unit time. Breast cancer ranks as the fifth cause of death from cancer overall, although still the leading cause of cancer mortality among women. It is estimated that mortality from breast cancer was 373,000 and which is approximately 14% of all cancer deaths (Parkin et al., 2001). Breast cancer is the second leading cause of cancer mortality among US women (American Cancer Society, 2002). According to Global Cancer Statistics report of 2002, the age-standardized mortality rates are higher (>20 per 100,000 women) among Northern and Western European populations (Table 2.1).
Table 2.1 Breast Cancer Incidence and Mortality Rates

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern America</td>
<td>99.4</td>
<td>19.2</td>
</tr>
<tr>
<td>Western Europe</td>
<td>84.6</td>
<td>22.3</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>84.6</td>
<td>19.4</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>82.5</td>
<td>22.6</td>
</tr>
<tr>
<td>Southern Europe</td>
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</tr>
<tr>
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<td>15.1</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>42.6</td>
<td>17.9</td>
</tr>
<tr>
<td>Micro/Polynesia</td>
<td>41.6</td>
<td>19.4</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>33.4</td>
<td>16.3</td>
</tr>
<tr>
<td>Western Asia</td>
<td>33.3</td>
<td>14.3</td>
</tr>
<tr>
<td>Caribbean</td>
<td>32.9</td>
<td>12.7</td>
</tr>
<tr>
<td>Japan</td>
<td>32.7</td>
<td>8.3</td>
</tr>
<tr>
<td>Western Africa</td>
<td>27.8</td>
<td>19.6</td>
</tr>
<tr>
<td>Central America</td>
<td>25.9</td>
<td>10.5</td>
</tr>
<tr>
<td>South Eastern Asia</td>
<td>25.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Northern Africa</td>
<td>23.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Melanesia</td>
<td>22.1</td>
<td>10.5</td>
</tr>
<tr>
<td>South Central Asia</td>
<td>21.8</td>
<td>11.1</td>
</tr>
<tr>
<td>Eastern Africa</td>
<td>19.5</td>
<td>14.1</td>
</tr>
<tr>
<td>China</td>
<td>18.7</td>
<td>5.5</td>
</tr>
<tr>
<td>Middle Africa</td>
<td>16.5</td>
<td>12.2</td>
</tr>
</tbody>
</table>

*Age-standardized Rates per 100,000 women; Source: Parkin et al., 2005.

The incidence of breast cancer is increasing almost everywhere. Breast cancer incidence is increasing rapidly in middle and low-income countries, including Asia, Africa and Latin America. On the other hand, mortality is now decreasing in many high-risk countries including North America, Western Europe and Australia. This decreasing trend in mortality could be due to a combination of intensified early detection efforts and
the introduction of mammographic screening, resulting in the diagnosis of more small, early stage tumors, and advances in treatment (Parkin and Fernandez 2006). Thus overall the incidence rate is increasing where as mortality rates are decreasing worldwide.

2.1.2. Indian scenario

It has been estimated that in 2001 there were approximately 80,000 new breast cancer patients in India. The disease is the commonest cancer among women in Delhi, Mumbai, Bhopal, Bangalore (NCRP, 2006) and Trivandrum (PBCR, Trivandrum 2005) registries and has overtaken cervix cancer, which was the commonest cancer a decade ago. It is the leading site of cancer in all cancer registries except in Barshi where breast cancer is listed as the second leading site among women. This disease accounted for 19-34% of all cancer cases among women nationally. Age-standardized incidence rates of breast cancer vary between 8-29 per 100,000 women (NCRP, 2006). Breast cancer incidence rates (age-standardized) among females across the various population based cancer registries in India are provided in Table 2.2 (Map of cancer registries in India- Appendix 1). The highest rate in India was reported in Trivandrum (urban) (31 per 100,000 women).

The cumulative incidence (the incidence of breast cancer calculated over a period of time during which all of the individuals are considered to be at risk for the development of disease) of breast cancer up to the age of 74 years is 2-3%. Thus in India 1 out of 30 to 42 women would develop breast cancer during her lifetime.

The age-standardized mortality rates (ASMR) for breast cancer across the different cancer registries in India are provided in Table 2.2. The highest mortality was observed in Chennai with an ASMR of 7.1 per 100,000 women followed by Bangalore (with an ASMR of 5.5 per 100,000 women) (NCRP 2006). However, currently the site-specific mortality information is challenging in India because of inadequate information systems to collect reliable data on causes of death.
Table 2. Breast cancer incidence and mortality rates in India (2001-2003)

<table>
<thead>
<tr>
<th>Cancer registries</th>
<th>Incidence rate*</th>
<th>Mortality rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trivandrum, urban</td>
<td>30.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Trivandrum, rural</td>
<td>19.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Bangalore</td>
<td>27.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Barshi</td>
<td>9.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Bhopal</td>
<td>22.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Chennai</td>
<td>26.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Delhi</td>
<td>29.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Mumbai</td>
<td>27.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Ahmedabad</td>
<td>7.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

* Age-standardized rates per 100,000 females; Sources: NCRP, 2006; $- PBCR, Trivandrum 2005.

Age-specific incidence rates of breast cancer reported in various cancer registries in India are provided in Table 2.3. In Trivandrum urban population, the highest age specific incidence rate of 111.8 per 100,000 women was observed in the age group 70-74 years (PBCR, Trivandrum 2005). Based on the national cancer registry report, Bangalore registry also reported the highest age specific incident rate of 110.4 per 100,000 women in the same 70-74 age groups (NCRP 2006). Further in all age groups above 35 years, breast cancer is the leading cancer among females in Trivandrum (PBCR, 2005).

2.1.3. Kerala scenario

Breast cancer is the first leading cancer among females in Kerala. At the Regional Cancer Center (RCC), Trivandrum, a total of 1386 breast cancer cases were reported in the year 2006, which accounts for 31% of all cancers among females. The frequency distribution of breast cancer cases registered at RCC for treatment according to the various demographic factors is provided in Table 2.4. The highest number of cases was observed in the age group 45-49 years (18%). Fifty three percent of cases had education secondary school or higher. Seventy nine percent of cases were married. Mother tongue was Malayalam for 88% of cases.
<table>
<thead>
<tr>
<th>Age group</th>
<th>Trivandrum urban</th>
<th>Trivandrum rural</th>
<th>Bangalore</th>
<th>Barshi</th>
<th>Bhopal</th>
<th>Chennai</th>
<th>Delhi</th>
<th>Mumbai</th>
<th>Ahmedabad</th>
</tr>
</thead>
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<tr>
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</tr>
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<td>0.2</td>
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<td>0.1</td>
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<td>1.1</td>
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<td>3.9</td>
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<td>9.5</td>
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<td>22.8</td>
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<td>5.3</td>
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<td>44.9</td>
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<td>60.4</td>
<td>71.5</td>
<td>65.9</td>
<td>62.1</td>
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<td>50-54</td>
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<td>100.0</td>
<td>89.5</td>
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<td>105.3</td>
<td>94.2</td>
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<td>99.2</td>
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<td>73.9</td>
<td>94.7</td>
<td>98.0</td>
<td>98.1</td>
<td>36.8</td>
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<tr>
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<td>17.6</td>
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<td>95.6</td>
<td>86.8</td>
<td>98.1</td>
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<td>77.7</td>
<td>11.1</td>
<td>30.4</td>
<td>65.0</td>
<td>75.2</td>
<td>109.2</td>
<td>16.2</td>
</tr>
</tbody>
</table>

Sources: NCRP, 2006; $-$ PBCR, Trivandrum report 2005;
* rates per 100,000 women in the respective age-group.
Table 2.4. Frequency distribution of breast cancer by demographic factors
Regional Cancer Center, Trivandrum (2006).

<table>
<thead>
<tr>
<th>Demographic factors</th>
<th>Categories</th>
<th>Number (n=1386)</th>
<th>Percentage</th>
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<tbody>
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</tr>
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<td>20-24</td>
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<td>0.6</td>
<td></td>
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<td>25-29</td>
<td>22</td>
<td>1.6</td>
<td></td>
</tr>
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<td>30-34</td>
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</tr>
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</tr>
<tr>
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<td>Others &amp; unknown</td>
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</table>

2.2. Risk factors of breast cancer

Factors that are associated with an increased chance of developing a disease of interest are known as risk factors, where as those associated with a decreased chance of developing the disease of interest are known as protective factors. Several factors have been identified or suspected to increase or decrease the risk for development of breast cancer in women. Having several risk factors does not mean that one will get breast cancer. On the other hand, not having any risk factors does not eliminate one’s chances of getting breast cancer.

Risk factors are identified by various epidemiological study designs like case-control study, cohort study and randomized controlled trail. Both case-control as well as cohort study designs are observational studies; where as randomized controlled trails are experimental study design. Case-control studies are well suited for rare diseases or diseases with longer incubation period (the interval between exposure to a carcinogen and clinical appearance of symptoms and signs of disease). For such studies, cases are subjects with a given disease and controls are subjects without the given disease and their past exposure is assessed and the exposure status of the two groups are compared for the development of disease. In cohort studies, disease free subjects are followed over time based on the exposure status and observe how many of them develop the disease of interest. Randomized controlled trails are experimental study design, where exposure is referred to as “intervention” or “treatment” and comparison are made between groups that do and do not receive the experimental intervention, in which subjects are assigned at random. However evidence from an experimental study is considered the strongest evidence, as it is subjected to less bias, when compared to other study designs.

Established risk factors of breast cancer included nulliparity (no children), late age at first child birth, early age at menarche, late age at menopause, less breastfed duration; anthropometric factors like increased body mass index (BMI) or overweight or obesity, increased body fatness, reduced physical activity, genetic and family history of cancer, use of exogenous estrogen and oral contraceptives, benign breast diseases and
exposure to ionizing radiation. Dietary factors such as increased consumption of diary products and meat and decreased consumption of fruits and vegetables are reported as risk factors for the development of breast cancer. The strength of the evidence of most of these factors including diet and risk of breast cancer has been assessed by an expert panel of the World Cancer Research Fund (WCRF), in association with the American Institute for Cancer Research (WCRF, 2007).

Risk factors of breast cancer differ by menopausal status (pre-menopausal and post-menopausal). WCRF summarized that body fatness, adult height gain among post-menopausal women and alcohol consumption irrespective of menopausal status were found to be convincing evidences for elevated risk of breast cancer; whereas lactation is inversely associated with breast cancer. Adult weight gain and abdominal body fatness among post-menopausal women and greater birth weight and adult height gain among pre-menopausal women were shown probable evidence for elevated risk of breast cancer. Further body fatness among pre-menopausal and increased physical activity among post-menopausal women found to be probable protective factors for breast cancer development (WCRF, 2007).

Risk estimates associated with the development of breast cancer according to the specific risk factors are provided in the subsequent session.

2.2.1 Age

Age is an important factor in determining a women’s risk for development of breast cancer. It has been reported that the incidence of breast cancer increases with age and the risk is doubling about every 10 years until the menopause, when the rate of increase slows dramatically (McPherson et al., 2000).
2.2.2 Genetic and familial aspects

Familial breast cancer accounts for approximately 5-10% of all breast cancers. One of the explanations for the familial aspect of breast cancer is the influence of genetic factors. Breast cancer risk is higher among women whose close blood relatives have the disease. Several epidemiological studies found increased breast cancer risk among women whose close blood relatives have the disease. It has been well recognized that female first degree relatives especially mothers and sisters of women with breast cancer, have two to three-fold risk of breast cancer compared to the general population (Kruk et al., 2007; Naieni et al., 2007; Yavari et al., 2005; Norsa'adah et al., 2005; ESHRE Capri Workshop Group 2004; Ebrahimi et al., 2002; Kishk 1999; Hirose et al., 1997). Family history of breast cancer has shown to be a stronger risk factor for pre-menopausal women (Faheem et al., 2007, Okobia et al., 2006; McCredie et al., 1998, Tavani et al., 1997).

Mutation plays a major role in the etiology of breast cancer. Mutations occur when the nucleotide sequence [Nucleotides are the structural units of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA)] of the genetic material of an organism changes, which can be caused by copying errors in the genetic material during cell division. Established genetic risk factors for breast cancer include germline mutations in genes such as BRCA1 and BRCA2. Studies have reported population proportion of germline mutations of these genes. In French-Canadian population, the combined population proportion of breast cancer susceptibility genes BRCA1 and BRCA2 was reported a frequency of about 1.2 per 1,000 women (Antoniou et al., 2006a). About 35% of women with a BRCA1 gene defect and 50% of those with a BRCA2 gene defect would be expected to develop breast cancer by the age of 70 years (Antoniou et al., 2006a). Further Friedman and Kramer (2005) claimed that women with BRCA1/BRCA2 mutations might increase the risk for developing breast cancer by becoming pregnant at late ages. The role of BRCA1 and BRCA2 in non-familial breast cancer is not clear and the number of carriers of these susceptibility genes in the general population is low. However, the effect of parity in BRCA1 and BRCA2 carriers has been studied by Narod (2006) and found that multi-parity appears to be protective in BRCA1 carriers.
A few genetics studies for assessing breast cancer risk observed that women with BRCA1 mutations who breast-fed for a cumulative total of more than 1 year had a statistically significantly reduced risk of breast cancer (Jernstrom et al., 2004). Another study in Central Sudan reported that BRCA1 and BRCA2 mutations represent important etiological factors of breast cancer in young women with less exposure to pregnancy and lactation (Awadelkarim et al., 2007). Further it is reported that increasing age at first childbirth was associated with an increased breast cancer risk among BRCA2 mutation carriers (p=0.002) but not BRCA1 carriers (Antoniou et al., 2006).

### 2.2.3 Exogenous estrogen

Simply being a woman is the main risk factor for developing breast cancer because their breast cells are constantly exposed to the growth promoting effects of the female hormones estrogen and progesterone. A reduction in lifetime exposure to estrogen due to late menarche, early menopause, bearing children and early pregnancy, may lead to reduction in risk of hormone related breast cancer. Age at menarche and menopause are closely associated to nutritional intake, with high-energy diets leading to early menarche and late menopause.

A few studies have investigated the association between lifestyle factors of breast cancer in relation to Estrogen Receptor (ER) and Progesterone Receptor (PR) status. The contribution of hormone receptor status for the development of breast cancer has been studied in India and revealed that significantly high incidence of breast cancer occur in ER negative (-) group (Desai et al., 2000). Lifetime physical activity in pre-menopausal as well as post-menopausal women had a protective effect for receptor-positive and receptor-negative breast cancers (Adams et al., 2006). Studies reported that reduced parity and late age at first childbirth were most consistently associated with increased breast cancer risk for ER+ than ER- tumors (irrespective of PR status) (Althuis et al., 2004). It is also reported that parous women, who lactated, were at decreased risk for ER-/PR- tumors (Largent et al., 2005). One of the largest population-based case-control
study, the Women’s CARE Study, on White and African-American women in the United States investigated the role of lifestyle factors on breast cancer risk in relation to hormone receptor status, and observed that women with at least five full-term pregnancies conferring 58% reduction in risk of ER+/PR+ tumours and also increased duration of breast feeding shown significant reduction for both receptor positive and receptor negative breast cancer (Ursin et al., 2005). Althuis et al. (2004) reported that early menarche was more consistently associated with ER+/PR+ than ER-/ PR- tumors.

An increase in proportion of ER+ breast tumour has also been found after the exposure of estrogen. Significantly higher hormone receptor positivity among the oral contraceptive users of breast cancer patients, irrespective of menopausal status was reported (Tewari et al., 2007).

Epidemiological studies such as observational studies and randomized controlled trails on the use of hormone replacement therapy (HRT) have been shown to increase the breast cancer risk (Lee et al., 2006; Gertig et al., 2006; Rossouw et al., 2002; Collaborative Group on Hormonal Factors in Breast Cancer 1997).

A few studies have reported a small elevation in risk associated with any use of estrogen (Kuhl et al., 2005; Kaaks et al., 2005). Long-term use of exogenous estrogens provided an increased risk of post-menopausal breast cancer in some studies (Chen et al., 2004; Chacko et al., 2004) while others reported no association (Tehard and Clavel-Chapelon 2006; Fournier et al., 2005; Anderson et al., 2004; Kliukiene et al., 2004). In clinical studies, exposure of exogenous estrogens found an increased risk of breast cancer in BRCA1 mutation carriers (Pujol et al., 2004). A significantly increased breast cancer risk was observed in relation to prolonged exposure to estrogens prior to the first full-term pregnancy (Lin et al., 2004). Therefore, various reproductive factors in the general population may influence the development of breast cancer.
2.2.4 Reproductive factors

The role of reproductive factors in the etiology of breast cancer has long been recognized. Numerous studies have been conducted in western populations to identify various reproductive risk factors associated with breast cancer. Women, who start menstruating early in life, having a late menopause, have an increased risk of developing breast cancer in most case-control studies. This 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).

2.2.4.1 Age at menarche

Early age at menarche has been observed as the single most important contributor to breast cancer incidence, with a population attributable risk of 44%, among women younger than 40 years of age (Gao et al., 2000). It has been established that approximately 20% reduction in breast cancer risk results from each year that menarche is delayed. For a fixed age at menarche, women who establish regular menstrual cycles within 1 year of their first menstrual period have more than double the risk of breast cancer compared to women with a 5-year or longer delay in the onset of regular cycles. Several studies have reported that early age at menarche was associated with increased risk of breast cancer (Velie et al., 2005, 2006; Gao et al., 2000; Kishk 1999; McCreedie et al., 1998; Tavani et al., 1997; Henderson et al., 1996). Among them one study was exclusively among post-menopausal women (Velie et al., 2005-2006). Women with age at menarche of 12 years or less and rapid establishment of regular cycles have an almost four-fold increased risk of breast cancer when compared to women with late menarche of age 13 years or older and long duration of irregular cycles (Henderson et al., 1996). An increased breast cancer risk was observed for women with early age at menarche before 13 years among post-menopausal women (Tung et al., 1999). Some studies have reported relatively weak association for early age at menarche among women below 45 years of age (Swanson et al., 1996). However, a meta-analysis published in 2006 found more
convincing evidence on the fact that age at menarche was inversely associated with the risk of breast cancer (Ma et al., 2006).

2.2.4.2 Age at menopause

It has been estimated that women who experience natural menopause before age 45 have only one-half the breast cancer risk of those whose menopause occurs the after age of 55 years (Gao et al., 2000; McPherson et al., 2000; Trichopoulos et al., 1972). Some more studies also reported that late age at menopause was positively associated with the risk of breast cancer (Naieni et al., 2007; Yavari et al., 2005; Talamini et al., 1996). Further it is reported that women with family history of breast cancer on first degree relatives, and late age at menopause had an elevated risk of breast cancer (Enger et al., 1998). Artificial menopause, by either bilateral oophorectomy or pelvic irradiation, also markedly reduces breast cancer risk (Lewis 2000).

2.2.4.3 Nulliparity and late age at first childbirth

Nulliparity and late age at first childbirth are the most consistently observed reproductive risk factors of breast cancer. The risk of breast cancer among women who have their first childbirth after the age of 30 is about twice that of women who have their first child before the age of 20. Several epidemiological studies on nulliparity and late age at first childbirth found consistent positive association for the development of breast cancer (Huo et al., 2008; Faheem et al., 2007; Okobia et al., 2005; Nichols et al., 2005; Tamakoshi et al., 2005; Neale et al., 2005; Yavari et al., 2005; Norsa'adah et al., 2005; Ursin et al., 2004; Althuis et al., 2004; Kuru et al., 2002; Gao et al., 2000; McPherson et al., 2000; Tung et al., 1999; Wohlfahet et al., 1999; Ramon et al., 1996). Among them, a large population based case-control study among white and African-American women in the United States observed that women who had ever been pregnant and experienced a full-term pregnancy, had 28% reduction of breast cancer risk in younger white women of ages 35 to 49 years and 23% reduction in the older white women of ages 50 to 64 years compared to women who never been pregnant (Ursin et al., 2004).
Among parous women, a significantly elevated breast cancer risk was observed with late age at first childbirth and low parity (Nichols et al., 2005; Tamakoshi et al., 2005; Wohlfahet et al., 1999). Gilliland et al. (1999) observed that parity and age at first childbirth were independently associated with the risk of breast cancer among Hispanic women. Some studies have reported no association between breast cancer risk and late age at first childbirth (Huo et al., 2008; Shantakumar et al., 2007).

2.2.4.4 Breast-feeding

Extensive breast-feeding may reduce the risk of breast cancer by suppressing the number of ovulatory cycles; however the evidence based on studies conducted in western populations is unclear (Lipworth et al., 2000). Lactation has been increasingly reported to protect against breast cancer development (Huo et al., 2008; Shantakumar et al., 2007; Naieni et al., 2007; Shema et al., 2007; Faheem et al., 2007; Kruk 2007; Okobia et al., 2006; Largent et al., 2005; Ursin et al., 2004; Gilliland et al., 1999). A study conducted among younger parous white and African-American women, of age between 35 and 49 years, who had given birth within the past 5 years and had breastfed for at least 24 months had a 62% reduction in risk compared with those who had not breastfed at all (Ursin et al., 2004). Some studies observed statistically significant protective association among post-menopausal women only (Okobia et al., 2006). A few studies have observed no association between duration of breastfeeding and subsequent risk of breast cancer (Yavari et al., 2005; Kishk 1999). A pooled analysis of epidemiological studies recently reported that long term breast-feeding was inversely associated with the risk of breast cancer (Ma et al., 2006).

2.2.5 Physical activity

Physical activity has been strongly suggested to reduce breast cancer risk among pre-menopausal and post-menopausal women independent of its effect on obesity, possibly by reducing estrogen production and influencing age at menarche and menopause.
Vainio and Bianchini (2002) reported that physical activity protects against breast cancer through reduced lifetime exposure to sex steroid hormones, reduced exposure to insulin and insulin-like growth factors, and prevention of overweight and obesity.

Numerous studies have assessed the association between physically strenuous activities and subsequent risk of breast cancer. Although most studies have reported that increased physical activity is associated with decreased risk, some reported no relationship. The inconsistencies in various studies may be attributable to differences in physical activity assessment methods used for measuring household, occupational and recreational activities. The critical time periods in life with respect to physical activity and development of breast cancer are quite unknown. However a longer duration of physical activity provides maximum benefit and such activity does not need to be strenuous (McTiernan et al., 2003).

The majority of the case-control studies focused on physical activity levels and breast cancer risk among post-menopausal women (Steindorf et al., 2003; John et al., 2003; Matthews et al., 2001; Friedenreich et al., 2001; Verloop et al., 2000). Some of these studies found a significant reduction of breast cancer risk ranging from 20% to 53% with a dose-response relationship (John et al., 2003; Matthews et al., 2001; Verloop et al., 2000). A population based breast cancer case–control study conducted in Shanghai between age 25 and 64 years, reported 20–40% reduction in breast cancer risk among women who had lifetime average of more than one hour per day of standing or walking at work, and a reduction of 53% among women who had exercise during adolescence and adulthood (Matthews et al., 2001). Results of cohort studies on total physical activity and breast cancer risk found to be inconsistent (Lahmann et al., 2007; Tehard et al., 2006; Fraser et al. 1997; Dorgan et al., 1994). Among the cohort studies, some reported decreased risk of breast cancer (Lahmann et al., 2007; Fraser et al., 1997) and some studies reported no association between total physical activity level and risk of breast cancer (Tehard et al., 2006).
Case-control studies on leisure time physical activities reported a protective association in most of the studies (Bernstein et al., 2005; Steindorf et al., 2003; Carpenter et al., 2003; Gilliland et al., 2001; Adams-Campbell et al., 2001; Matthews et al., 2001; Verloop et al., 2000; Levi et al., 1999; Ueji et al., 1998). Some of these studies reported a clear evidence of dose-response relationship (Steindorf et al., 2003; Adams-Campbell et al., 2001; Matthews et al., 2001; Levi et al., 1999; Ueji et al., 1998). More over some cohort studies assessed leisure time physical activities for assessing the breast cancer risk reported protective association for the development of breast cancer (McTiernan et al., 2003; Wyrwich and Wolinsky 2000, Patel et al., 2003; Breslow et al., 2001; Cerhan et al., 1998; Sesso et al., 1998; Thune et al., 1997). A few case-control (Tehard et al., 2006; Moore et al., 2006; Colditz et al., 2003; Dirx et al., 2001; Moradi et al., 2000) and some cohort studies (John et al., 2003; Moradi et al., 2002; Hu et al., 1997; McTiernan et al., 1996) reported no significant association. However a recently published review article summarized that the observational studies shown strong evidence for a protective effect for physical activity among post-menopausal women with risk reductions ranging from 20% to 80%, where as for pre-menopausal women, the evidence seems to be much weaker (Monninkhof et al., 2007).

2.2.6 Anthropometric factors

A number of epidemiological studies investigated the role of anthropometric factors such as body mass index (BMI), waist-to-hip ratio (WHR) and early/adulthood/lifetime weight gain in relation to breast cancer development. Majority of the studies have reported that overweight or obese women have increased risk of developing breast cancer in post-menopausal women (Iwasaki et al., 2007; Palmer et al., 2007; Kruk 2007; Naieni et al., 2007; Li et al., 2006; Boyd et al., 2006; Rinaldi et al., 2006, b Tehard et al., 2006; Chow et al., 2005; Key et al., 2003; Lahmann et al., 2003). Some studies have reported no association between obesity and breast cancer risk (Dettenborn et al., 2008; Norsa'adah et al., 2005).
Increased body fat and weight gain in most studies have predicted the risk of breast cancer in post-menopausal women. Well known Malmö Diet and Cancer Study assessed the body fat distribution among 12,159 Swedish post-menopausal women in association with breast cancer incidence and observed 2-fold (100%) higher risk among those women with the highest level of body fatness; and 54% higher risk of breast cancer with increased BMI in the highest quintile compared to lean women (Lahmann et al., 2003). A clear evidence of an elevated risk of breast cancer among Canadian post-menopausal women observed in association with increased BMI in the highest quartile level of energy intake (Silvera et al., 2006). Among pre-menopausal women, the relationship between BMI and breast cancer risk are less consistent (Kruk 2007; Carmichael and Bates 2004; Adderley-Kelly and Williams-Stephans 2003; Stevens et al., 2002).

Some studies have reported overweight (BMI ≥ 25) at early years of life (< age 18 years) was associated with a significant reduced risk of breast cancer among both pre- and post-menopausal women (Palmer et al., 2007); where as weight gain since age 20 found significantly associated to an elevated risk for post-menopausal breast cancer (Li et al., 2006; Lahmann et al., 2003). The risk associated with increased body weight was observed among non-users of hormone replacement therapy (HRT) (Mellemkjaer et al., 2007) and among all women irrespective of HRT (Wu et al., 2007). A recent study among post-menopausal women found that BMI and weight gain during adulthood were associated with increased breast cancer risk, particularly in women not using menopausal hormone therapy (Ahn et al., 2007).

A number of studies have been reported positive association between increased waist circumference or WHR and breast cancer risk among post-menopausal women (Li et al., 2006; Okobia et al., 2006; Tehard and Clavel-Chapelon 2006; Rinaldi et al., 2006; Harvie et al., 2003) as well as in pre-menopausal women (Mannisto et al., 1996). Some studies have shown elevated risk with increasing WHR irrespective of menopausal status (p-trend = 0.04) (Wu et al., 2007).
Rapid growth in early years (Velie et al., 2005-2006; Shu et al., 2001; AICR 1997), weight gains during adulthood and lifetime weight gain (Han et al., 2006; Lahmann et al., 2003) have all been reported to be associated with increased breast cancer risk among post-menopausal women.

2.2.7 Oral contraceptives

The collaborative group on hormonal factors in breast cancer (1996) based on 54 studies worldwide concluded that among women who are taking oral contraceptives (OCs), there is a small but definite increase in the risk of breast cancer relative to non-users. However the risk declines after stopping use and no increase in relative risk was found 10 years after stoppage. Exposure to OCs potentially increases the risk of early-onset breast cancer (Kruk 2007; Friedman and Kramer, 2005; Yavari et al., 2005 Norsa'adah et al., 2005). A recent study among Polish women observed an increased breast cancer risk among pre-menopausal OC users compared to non-users (Kruk et al., 2007). The study reported that ever use of OCs before first full-term pregnancy compared with never users was more strongly associated with breast cancer risk of 1.44 fold than ever use after first full-term pregnancy (OR:1.15; 95% CI:1.06-1.26). Women with a family history of breast cancer in first-degree relatives have shown increased risk of breast cancer but there is no evidence to suggest that this differs according to a woman's use of OC or menopause hormone treatment (ESHRE Capri Workshop Group 2004). Previous exposure of OCs among post-menopausal women reported no association with breast cancer risk, while some women may develop breast cancer soon after OCs exposure, leading to a deficit of cases of older women (Faheem et al., 2007; Dumeaux et al., 2005). A meta-analysis of 34 case-control studies assessed the relationship between OC use and pre-menopausal breast cancer found that OC use was significantly associated with an increased risk of breast cancer (OR: 1.19; 95% CI: 1.09-1.29) (Kahlenborn et al., 2006).
2.2.8 Benign breast diseases

Multiplicity of benign breast disease (BBD) lesions in a biopsy is considered to be a risk factor for progression to breast cancer. The most common type of BBD is fibrocystic disease. Women with fibrocystic breast disease have a two to five-fold increased risk of developing breast cancer (Hartmann et al., 2005; Marshall et al., 1997). Also an increased risk of proliferative fibrocystic conditions was associated with low parity, a prior benign breast lump and breast cancer in first-degree relatives (Li et al., 2005).

Fibroadenoma is the second most common histologic type of benign breast disease. Coexistence of fibroadenoma and breast cancer is relatively rare, the extent of which however has not been well established (Markpoulos et al., 2004; Arihiro et al., 2002). However neither fibrocystic breast disease nor fibroadenoma, have shown a significantly higher prevalence rate in cases than in controls (Worsham et al., 2007; Soran et al., 2005; Franco et al., 2001). Although BBD lesion of either proliferative without atypia (atypia is a clinical term for abnormality in a cell, which may be a precancerous indication associated with later malignancy) or proliferative with atypia were reported to be significant risk factors for breast cancer (Worsham et al., 2007), some studies shown no elevated association (Berg et al., 2008). A positive family history of breast cancer slightly increased the breast cancer risk among women who had proliferative lesions without atypia (Collins et al., 2006). Breast cancer risk for woman with atypical lesions is significantly higher than for women with proliferative lesions without atypia (Worsham et al., 2007; Hartmann et al., 2005). Post-menopausal women with proliferative disease without atypia and women with atypical hyperplasia (hyperplasia is a general term referring to the proliferation of cells within an organ or tissue beyond that organ) had an increased risk of breast cancer compared to women who had non-proliferative benign breast disease (Byrne et al., 2000).

Benign breast biopsies of concurrent multiple benign lesions with different histopathologic diagnoses were known as heterogeneous benign breast disease (HBBD) and those women with higher risk of BBD lesions are more likely to have HBBD. However
teasing out the HBBD lesions found to be warranted to refine and improve risk estimates for progression of breast cancer from BBD (Worsham et al., 2007; Cheng et al., 2008).

Some studies have focused on genetic polymorphism to examine whether specific gene polymorphism are associated with the progression of BBD to breast cancer. A cohort study conducted among the Caucasian women, who had a breast biopsy for BBD, to examine the role of genetic polymorphisms in three estrogen metabolizing enzymes (COMT, CYP1A1, CYP1B1) and the two estrogen receptors (ESR1, ESR2) reported that CYP1B1, ESR1, and ESR2 genes may play a role in progression of BBD to breast cancer (Gallicchio et al., 2006). Another study from the same cohort among post-menopausal women, to determine the association of obesity-related genes (PPARG, LPL, LEPR, PON1, PON2, TNF-alpha), found that specific genetic polymorphisms in the PON1 and LEPR genes may play a role in progression of BBD to breast cancer (Gallicchio et al., 2007).

Definition of the varieties of BBD and their relationship with breast cancer should permit reliable identification of subgroups of the population of women with BBD.

2.2.9 Diet

Over the past 20 years there has been a great deal of research into the link between diet and breast cancer. Over all epidemiological studies of diet on any outcome of interest is quite complicated, as the dietary assessments may affect a lot of biases including inaccuracies in measurement of dietary items, inappropriate diet assessment methods, day-to-day variation in individual intake, recall bias, errors in quantification of individual consumption, nutrient loss during cooking and so on. Hence studies on dietary exposures for any outcome are challenging.

Studies conducted in the early eighties reported that diet related factors accounts for 10-70% of all cancer deaths in the US (Doll and Peto, 1981) and in the early nineties it is revised to 20-60% (Doll, 1992). Binukumar and Mathew in 2005 made a review of
seventeen case-control and twenty cohort studies (published between 1990 to 2003) to find the evidence on the association between consumption of fat and their effect on the development of breast cancer (Appendix 3). Increased consumption of total fat and saturated fat were found to be positively associated with the development of breast cancer. Several studies have reported that dietary factors such as increased consumption of alcohol, dairy fat and red meat, decreased consumption of fruits and vegetables were reported as associated factors for the development of breast cancer. Recent available evidence suggested that increased alcohol consumption associated with an elevated risk of breast cancer risk, where as increased intake of other factors such as fibre, fruits and vegetables, antioxidant, vitamins and phytoestrogens have been inconclusive (WCRF 2007).

The subsequent session focused on current available information on the consumption of various dietary factors such as dairy products, meat particularly red meat, white meat, processed meat, fruits and vegetables, and other dietary factors associated with the development of breast cancer.

2.2.9.1 Dairy products

The association between consumption of dairy products and subsequent risk of breast cancer has been investigated in many epidemiological studies. A few studies have reported that dairy products, particularly low fat products, might decrease the risk of breast cancer. Some studies have reported protective association with significant dose-response relationship on dairy product intake and breast cancer risk in pre-menopausal women (Kesse-Guyot et al., 2007; Shin et al., 2002) and in post-menopausal women (Kesse-Guyot et al., 2007; McCullough et al., 2005; Shannon et al., 2003). Experimental animal models suggested that the conjugated linoleic acid, a polyunsaturated fatty acid found in dairy fat, confers a wide range of anti-carcinogenic benefits and protects against breast cancer (Huth et al., 2006). However, recently published report by WCRF (2007) observed no clear evidence of an association between breast cancer risk and dairy products consumption. A number of epidemiological reviews also concluded that there is no clear evidence of a consistent association between the consumption of dairy products
and risk of breast cancer (Alvarez-León et al., 2006; Al Sarakbi et al., 2005; Parodi 2005; Moorman et al., 2004).

The Boyd Orr cohort (a 65-years follow-up study) study investigated the association between childhood dairy consumption and the cancer incidence and mortality in adulthood and found that childhood dairy intake was not associated with breast cancer risk (van der Pols et al., 2007). A pooled analysis of eight prospective cohort studies conducted in North America and Western Europe also found non-significant association between intake of solid dairy products and risk of breast cancer (Missmer et al., 2002). Hence it is still unclear whether eating dairy products affects a woman's risk of breast cancer, although high consumption of dietary fat found to be positively associated with post-menopausal breast cancer (Binukumar and Mathew 2005; WCRF 2007).

Some studies have examined the association of milk and cheese with the development of risk of breast cancer separately. Milk contains a wide variety of ingredients such as nutrients, hormones and chemical contaminants. A few studies reported significant protective association on consumption of milk and risk of breast cancer (Wirfält et al., 2005; Shin et al., 2002; Knekt et al., 1996). Among them one study on pre-menopausal women found that consumption of skimmed or low-fat milk was inversely associated with risk of breast cancer (Shin et al., 2002). Well-known Malmö Diet and Cancer cohort of Sweden observed that fat from fermented milk products observed to be inversely associated with post-menopausal breast cancer risk with significant dose-response pattern (Wirfält et al., 2005). Zhanj et al. (2005) investigated the role of milk consumption and breast cancer risk based on the data on milk consumption for nine time periods between 1964 and 1994 in 38 countries obtained from the Food and Agriculture Organization and World Health Organization. The study did not support an overall substantial effect of milk consumption on the risk of breast cancer, however, a good correlation (r= 0.64 -0.74; with p-values <0.001) was observed between milk consumption and breast cancer incidence rates in all the nine time periods examined.
Some studies have shown that women with high consumption of butter were associated with elevated risk of breast cancer (Frazier et al., 2003; McEligot et al., 2000), and some did not (Le et al. 1986). A case-control study during the period 1999-2001 investigated possible association of milk and the risk of breast cancer in Montevideo, found that high consumption of milk and gruyere cheese were associated with significant increased risk of breast cancer, where as ricotta cheese and skin yoghurt were associated with significant decreased risks (Ronco et.al., 2002). Another case-control study from France also reported elevated risk of breast cancer with increased frequency of cheese consumption and the level of fat in the milk consumed. An inverse association was also found between frequency of yogurt consumption and the risk of breast cancer (Lee et al., 1986).

2.2.9.2 Meat and fish

Meat consumption particularly red meat, white meat and processed meat possess a strong relationship with breast cancer. Red meats are defined to be red in color before cooking which include beef, venison and mutton; except pork. Even though pork is rather light coloured, it is still considered to be red meat. White meats are light coloured before cooking and it usually comes from poultry and seafoods. Processed meat has been grinded in order to make it more malleable, and generally has more preservatives. Processed meats include meats that are salted, cured, or smoked ones and also hamburgers; hot dog, bacon, sausage, salami, luncheon meat and other cured meats. They are usually high in fats and salt.

Many authors have looked for an association between breast cancer and the consumption of various meat products and their doneness levels (van der Hel et al., 2004; Dai et al., 2002; Delfino et al., 2000; Zheng et al., 1999; Gertig et al., 1999; Zheng et al., 1998). The association of breast cancer due to carcinogenic substances such as heterocyclic amines (HCA), polyaromatic hydrocarbons and the effects of metabolizing enzymes such as Glutathione S-transferases (GST) and N-acetyl transferases (NAT) from well-done meat have also been reported in some studies (van der Hel et al., 2004; Zheng
et al., 2002; Zheng et al., 2001; Deitz et al., 2000; Delfino et al., 2000; Sinha et al., 2000; Gertig et al., 1999).

Red meat

Several case-control studies reported significant positive associations between increased consumption of red meat and risk of breast cancer with dose-response relationships (Cui et al., 2007; Di Pietro et al., 2007; Kruk 2007; Brandt et al., 2004; Shannon et al., 2003; Hermann et al., 2002; Favero et al., 1998; Ronco et al., 1996), whereas cohort studies reported increased risk with non-significant association (Cho et al., 2003; Sala et al., 2000). Among these significant case-control studies, three were based on pre-menopausal women (Kruk 2007; Hermann et al., 2002; Lee et al., 1992). The UK Women's Cohort Study found a significant positive association with red meat consumption among post-menopausal women (Taylor et al., 2007). The Nurses' Health Study II (cohort study) also observed that increased red meat intake strongly related to elevated risk of breast cancer among pre-menopausal women who are estrogen and progesterone receptor positive (ER+/PR+), but not among estrogen and progesterone receptor negative (ER-/PR-) women (Cho et al., 2006). However, several studies reported no association between consumption of red meat and breast cancer risk (Nkondjock & Ghadirian, 2005; Fung et al., 2005; Sieri et al., 2004; Holmes et al., 2003; Hirose et al., 2003; Petro-Nustas 2002; Voorrips et al., 2002; Terry et al., 2001).

A few case-control studies reported association between doneness level of red meat intake and breast cancer risk (Dai et al., 2002; Delfino et al., 2000). Between them, one study reported a strong positive association (OR=1.92 for the highest quartile consumption) with significant dose-response relationships on increased consumption of well-done red meat (Dai et al., 2002). While considering the various cooking methods for the preparation of red meat, some cohort studies also reported significant positive associations (Zheng et al., 1999; Zheng et al., 1998). Increased, but non-significant breast cancer risk observed in one study (van der Hel et al., 2004) and another study reported no association (Gertig et al., 1999). A pooled analysis of eight cohort studies from North
America and Western Europe found non-significant positive association between red meat consumption and breast cancer (Missmer et al., 2002).

**White meat**

Among white meat, fish is considered as a source of high quality protein and contains all essential amino acids. Animal experimental studies have shown a protective effect of fish consumption on breast cancer risk, which is one of the reasons that recommend women to eat more fish. Among the case-control studies, a few studies on fish or seafood consumption reported protective effects of breast cancer (Hirose et al., 2003; Favero et al., 1998; Braga et al., 1997; Levi et al., 1993; Malik et al., 1993) with significant dose-response relationship (Hirose et al., 2003; Landa et al., 1994; Malik et al., 1993). A cohort study that investigated the breast cancer risk on fish consumption found that fish fat consumption reported a strong protective association with significant dose-response relationship among pre-menopausal women (Wakai et al., 2005). Decreased but a boarder line significance was also observed for the highest quartile consumption of fish (OR= 0.70, 95% CI: 0.4-1.0) among post-menopausal women (Ambrosone et al., 1998). Several cohort studies (Haldorsen & Tynes, 2005; Gago Dominiguez et al., 2003; Sala et al., 2000) as well as case-control studies (Terry et al., 2002) also reported reduced, but non-significant associations.

The European Prospective Investigation into Cancer and Nutrition (EPIC) study, the largest cohort study, examined the association between fish consumption and breast cancer risk using a food frequency questionnaire and 7-day food diary. After a median follow-up of 6.4 years, 4,776 became invasive incident breast cancer cases, observed that intake of total fish provided non-significant association of breast cancer risk; but when examined the association of lean and fatty fish separately, a positive significant association was found in the highest quintile for fatty fish (hazard ratio (HR) = 1.13, 95% CI: 1.01-1.26), with non-significant trend (p = 0.10) (Engeset et al., 2006).
Other epidemiological studies reported no association between consumption of fish and breast cancer risk (Shannon et al., 2005; Holmes et al., 2003; Cho et al., 2003; Shannon et al., 2003; Hermann et al., 2002; Key et al., 1999; Fernandez et al., 1999).

Some case-control studies investigated the role of chicken or poultry consumption and the risk of breast cancer. A reduced breast cancer risk (OR= 0.70) with significant dose-response relationship for increased consumption of white meat in post-menopausal women was reported (Ambrosone et al., 1998). Reduced risk (OR= 0.87) but non-significant association was observed in another study (Shannon et al., 2003). A few studies reported no association between breast cancer risk and increased consumption of chicken or poultry (Hirose et al., 2003; Levi et al., 1993).

Although lack of association between white meat intake (including fish, chicken and poultry together) and its subsequent risk of breast cancer observed in cohort studies, several case-control studies, reported decreased risk, but non-significant associations (Hermann et al., 2002; Ronco et al., 1996; Ingram et al., 1991). One case-control study (Potischman et al., 1998) and several cohort studies reported no association between breast cancer risk and the consumption of white meat (Shannon et al., 2005; Cho et al., 2003; Holmes et al., 2003; Terry et al., 2001; Sala et al., 2000; Key et al., 1999). A pooled analysis of eight cohort studies from North America and Western Europe found no significant association between intake of white meat with and breast cancer (Missmer et al., 2002).

The doneness level of white meat has been studied by a few epidemiological studies. A few case-control studies (Dai et al., 2002; Delfino et al., 2000) as well as cohort studies (van der Hel et al., 2004; Gertig et al., 1999) investigated the association between doneness level of white meat and breast cancer risk. Among the case-control studies, one study reported a positive association with significant dose-response relationship for the consumption of well-done fish or seafood with OR=1.66 (95% CI: 1.31-2.11) in the highest quartile (Dai et al., 2002). Contrary to the above positive association, increased consumption of well-done white meat reported a protective effect.
of breast cancer with significant dose-response relationship (Delfino et al., 2000). One cohort study on NAT2 from well-done fish reported increased, but non-significant associations (Gertig et al., 1999); where as reduced and non-significant association was observed for GSTM1 from well done white meat (van der Hel et al., 2004).

**Processed meat**

A few studies have concentrated on processed meat consumption and its effect on developing breast cancer. Among the case-control studies, Landa et al. (1994) observed statistically significant positive associations with dose-response relationship between the increased consumption of processed meat and subsequent risk of breast cancer. Increased risk, but non-significant associations have found in five studies (Shannon et al., 2003; Hermann et al., 2002; Ambrosone et al., 1998; Ronco et al., 1996; Richardson et al., 1991). Among the cohort studies, the UK Women's Cohort Study also observed a significant positive association between processed meat consumption and breast cancer risk (HR=1.64, 95% CI: 1.19-2.27) in post-menopausal women (Taylor et al., 2007). However, two cohort studies reported significantly decreased breast cancer risks with increased processed meat (Key et al., 1999; Vatten et al., 1990). Some cohort studies have shown no association between processed meat intake and breast cancer risk (Nkondjock & Ghadirian, 2005; Shannon et al., 2005; Fung et al., 2005; Holmes et al., 2003; Voorrips et al., 2002; Terry et al., 2001).

A few case-control studies have reported a reduced risk with increased consumption of dried/salted fish (OR=0.78) with dose-response relationship (p-trend=0.04) among post-menopausal women (Hirose et al., 2003). Also a significant protective effect was observed with increased consumption of raw ham observed (OR=0.70) for the development of breast cancer (Levi et al., 1993).

Studies focused on doneness levels of processed meat and breast cancer risk are very limited. Some cohort studies reported the association between doneness levels of processed meat and breast cancer risk. The specific groups of processed meat such as
well-done bacon, with a daily consumption of more than 0.07 servings, observed a significantly increased breast cancer risk (Gertig et al., 1999). Further, one study on consumption of processed meat (van der Hel et al., 2004) and another study on well-done bacon and hamburger (Zheng et al., 1998) found no associations.

2.2.9.3 Fruits and vegetables

Fruits and vegetables are an important component of a balanced, healthy diet. They possess fiber, vitamins and minerals and almost everyone can benefit from eating more of them, but variety are as important as quantity. No single fruit or vegetable provides all of these nutrients needed for healthy life. However it is unclear that which of these components may contribute to the potentially protective effect against some types of cancer, so taking supplements that contain the vitamins and minerals found in fruit and vegetables may not have the same impact on cancer risk.

Diets rich in fruits and vegetables have been recommended for preventing cancer. The evidence supporting this recommendation is based on observational studies, although results of several prospective studies, have cast some doubts on whether fruits and vegetables are associated with cancer risk reduction. However based on the limited evidence, WCRF (2007) didn’t draw any conclusion about the higher consumption of fruits and vegetables and the risk of breast cancer.

Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk sought to summarize evidence from case-control and prospective studies on fruit and vegetable intake and cancer risk with a meta-analytic approach. The pooled estimate of odds ratio from case-control studies supported that breast cancer is associated with consumption of vegetables but not with fruits. The overall relative risk estimates from cohort studies suggested a protective effect of both fruit and vegetable for most cancer sites considered, but the risk reduction was not significant for breast cancer (Riboli et al., 2003). Another meta analysis on cohort studies by Smith-Warner et al. (2001) observed weak, but borderline significant associations for total fruits (RR: 0.93; 95%CI: 0.86-1.00;
p for trend =0.08), and total fruits and vegetables (RR: 0.93; 95%CI: 0.86-1.00; P for trend= 0.12) and a non-significant association for total vegetables alone (RR: 0.96; 95%CI: 0.89-1.04; P for trend=0.54) for the development of breast cancer. Results suggested that fruit and vegetable consumption during adulthood was not significantly associated with reduced breast cancer risk.

**Fruits**

Several epidemiological studies investigated the role of fruit consumption for the development of breast cancer. Among them some case-control studies increased consumption of fruits found to have protective effect (Do et al., 2007; Ahn et al., 2005; Gaudet et al., 2004; Malin et al., 2003; Ronco et al., 1999; Trichopoulou et al., 1995). Among these studies one study focused on estrogen receptor status and found that an inverse association for fruits was stronger for post-menopausal women with ER+ tumors than ER- tumors (Gaudet et al., 2004). However a cohort study conducted among post-menopausal women reported a significant protective association on higher consumptions of fruits with significant dose-response relationship for ER- breast cancer (Fung et al., 2005). A few studies reported non-significant decreased associations (Adzersen et al., 2003; Shannon et al., 2003; Hirose et al., 2003; Silva et al., 2002; Thorand et al., 1998; Verhoeven et al., 1997). Significant dose-response relationship was observed in a few studies (Hirose et al., 2003; Ronco et al., 1999; Trichopoulou et al., 1995). A nested case-control study in Shanghai among women having fibrocystic breast conditions with and without concurrent breast cancer reported that decreased trends in the risk of both conditions with increased intake of fruits (Li et al., 2005). No association was observed in several cohort studies reported (Olsen et al., 2003; Adzersen et al., 2003; Sala et al., 2000; Key et al., 1999) as well as in case-control studies (van Gils et al., 2005; Hermann et al., 2002; Franceschi et al., 1995; Zaridze et al., 1991; Ingram et al., 1991).
Vegetables

Several case-control studies investigated the association between vegetables consumption and reported protective associations for the development of breast cancer (Do et al., 2007; Gaudet et al., 2004; Malin et al., 2003; Adzersen et al., 2003; Hirose et al., 2003; Silva et al., 2002; Hermann et al., 2002; Ronco et al., 1999; Trichopoulou et al., 1995). Among these studies Gaudet et al. (2004) investigated the role of estrogen receptor status and observed that an inverse association for vegetables is stronger for post-menopausal women with ER+ tumors than ER- tumors. As similar to the fruits consumption, number of cohort studies used to assess the risk of vegetables intake for the development of breast cancer is very less. However one cohort study on salad vegetables consumption provided a significant protective association (Sieri et al., 2004) and another study among post-menopausal women reported a significant protective association for ER(-) breast cancer women with higher consumption of vegetables (Fung et al., 2005). Significant dose-response relationship between increased vegetable consumption and breast cancer risk was found in some studies (Fung et al., 2005; Sieri et al., 2004; Adzersen et al., 2003; Hirose et al., 2003; Silva et al., 2002; Hermann et al., 2002; Ronco et al., 1999; Trichopoulou et al., 1995). Also a nested case-control study in Shanghai among women having fibrocystic breast conditions with and without concurrent breast cancer reported decreased risk with increased consumption of vegetables of both conditions (Li et al., 2005). A few studies provided non-significant decreased associations (Shannon et al., 2003; Olsen et al., 2003; Holmes et al., 1999; Thorand et al., 1998). No association was observed in a few studies (van Gils et al., 2005; Sala et al., 2000; Key et al., 1999; Verhoeven et al., 1997; Landa et al., 1994; Ingram et al., 1991; Zaridze et al., 1991).

Some case-control studies focused on consumption of raw vegetables and subsequent risk of breast cancer also reported protective associations (Adzersen et al., 2003; Ronco et al., 1999; Franceschi et al., 1995). Among them, two studies reported a significant dose-response relationship (Ronco et al., 1999; Franceschi et al., 1995). A few studies have reported no association (Hirose et al., 2003; Hermann et al., 2002).
2.2.9.4 Dietary fiber

Dietary fiber intake may protect against breast cancer by inhibiting deconjugation and reabsorption of estrogen from the colon (Gerber 1998). Some animal experiments reported that high fiber intake was associated with decreased mammary tumor incidence (Cohen et al., 1996). Several case-control studies have reported an inverse association between dietary fiber intake and breast cancer risk (Ronco et al., 1999; De Stefani et al., 1997; Howe et al., 1990), but data from prospective studies have not supported this association (Jarvinen et al., 1997; Verhoeven et al., 1997; Rohan et al., 1993). However, the UK Women's Cohort Study provided a statistically significant inverse relationship between total fibre intake and risk of breast cancer among pre-menopausal women only [HR: 0.48; 95%CI: 0.24-0.96 for the highest quintile consumption of dietary fiber compared with the lowest quintile] (Cade et al., 2007).

2.2.9.5 Alcohol consumption

The association between alcohol consumption and risk of breast cancer has been well established. Several cohort studies (Tjønneland et al., 2007; Zhang et al., 2007; Petri et al., 2004; Mattisson et al., 2004; Tjønneland et al., 2003) as well as case-control studies (Ibarluzea et al. 2004; Gallus et al. 2003; Atalah et al., 2000; Bowlin et al., 1997) investigated the relation between consumption of alcohol and the risk of breast cancer and observed statistically significant increased breast cancer risk for the highest consumption category compared to the lowest category of alcohol consumption. Among them, some studies have exclusively focused on breast cancer risk on post-menopausal women only (Tjønneland et al., 2007; Tjønneland et al., 2004; Mattisson et al., 2004, Tjønneland et al., 2003). A recent result published from EPIC cohort study observed a risk estimate of 1.03 (95% CI: 1.01-1.05) for consumption of 10g/day higher recent alcohol intake compared to non-users (Tjønneland et al., 2007).

The wellknown Women's Health Study of United States also found an elevated risk of invasive breast cancer on increased alcohol consumption [Relative risk (RR)=1.43 (95% CI: 1.02- 2.02) for ≥ 30 g/day of alcohol vs. none] (Zhang et al., 2007). Further
increased consumption of wine was associated with a significantly elevated breast cancer risk (RR= 2.12, 95% CI 1.24-3.60) (Mattisson et al., 2004). A non-significantly elevated risk was observed for high total alcohol intake among post-menopausal women (Mattisson et al., 2004).

A meta-analysis of epidemiologic studies carried out to examine the dose-response relation between alcohol consumption and risk of breast cancer observed a monotonic increase in the risk of breast cancer. However a risk estimate of 1.10 (95% CI: 1.06-1.14) was found for alcohol consumption of 12 g/day, as compared to no users (Ellison et al., 2001). Further this study revealed that the risk estimates were 7% greater in hospital-based case-control studies than in cohort studies or community-based case-control studies.

2.2.10. Other factors

Factors such as environmental pollutants such as exposure to pesticide, organochlorines and ionizing radiations and cigarette smoking are also influence the development of breast cancers (Cohn et al., 2007; Brody et al., 2007; Laden and Hunter 1998). All these factors have relevant importance in the etiology of breast cancer.