Chapter 1
Introduction
1.1 Biology of Breast Cancer

1.1.1 Anatomy of Breast

The adult breast sits atop the pectoralis muscle, atop the ribcage. The breast tissue extends horizontally (side-to-side) from the edge of the sternum out to the midaxillary line. There are about 15 to 20 lobes in each breast [1]. Each lobe has 20 to 40 lobules. Small ducts are attached to the lobules. These ducts join together like branches of grape stems into increasingly larger ducts. There are about 10 duct systems in each breast, each with its own opening at the nipple [2] (Figure 1.1).

Figure 1.1: Structure of the Breast

The breasts can be divided into quadrants for purposes of location of abnormalities. The four quadrants are the:

- UIQ: Upper Inner Quadrant
- LIQ: Lower Inner Quadrant
- UOQ: Upper Outer Quadrant
- LOQ: Lower Outer Quadrant
The exact locations within the quadrants can be represented by viewing each breast separately as a clock face. The majority of Breast Cancer (BC) occur in the upper outer quadrant of the breast.

The blood supply to the breast is derived from 3 sources. The predominant supply of blood comes from the perforating branches of the internal mammary arteries, derived from the internal thoracic artery. The breast is further supplied by the lateral thoracic and thoracoacromial arteries (branches of the axillary artery) as well as posterior intercostal arteries (branches of the thoracic aorta).

Venous drainage of the breast is mainly accomplished by the axillary vein. The subclavian, intercostal, and internal thoracic veins also aid in returning blood to the heart.

The lymphatic drainage of the breast deserves special attention, due to its role in the metastasis of cancer cells. The majority of lymph (>75%), particularly from the lateral quadrants, drains to the axillary lymph nodes. The remainder of lymph drains to either the parasternal nodes or the opposite breast (medial quadrants) or the inferior phrenic nodes (lower quadrants). With the exception of the nipple and areola, lymph from the skin of the breast drains into the axially, inferior deep cervical, infraclavicular, and parasternal nodes (depending on the location of the vessel) [3].

1.1.2 Tumour size and lymph node involvement

Tumour size is defined as the largest diameter of the tumour and is a prognostic factor for BC death regardless of other tumour characteristics [4,5]. Lymph node involvement is another important independent prognostic factor [5]. Women with lymph node involvement have poorer prognosis compared to women without lymph node involvement, and increasing number of affected lymph nodes are associated with poorer prognosis. Tumour size and lymph node involvement are correlated, and none of them seems to be predictive of treatment effect [6].
1.1.3 Morphology

Breast tumours are almost exclusively adenocarcinomas. Rarely, sarcomas or lymphomas develop, but these tumours are generally excluded when studying BC. The morphology of the breast tumour has been in clinical use for a long time, and current classifications are modifications from the classification made by Fraser in 1927 [7]. They are simply classified by their morphological appearance in the microscope. Still, the underlying carcinogenesis resulting in different histological types is largely unknown, and combinations between different types are common.

The two most common histological types of BC are derived from the breast glandular ducts and lobules, respectively. Ductal tumours make up the majority of BCs, and lobular cancers compose 5-15% of BCs [8]. Compared to ductal cancer, lobular cancer is more common among older women and is more often ER+, multifocal and bilateral. The metastatic pattern is also somewhat different. Despite these differences, ductal and lobular BC have similar prognosis [9,10]. There are also other rarer but well-defined histological types of BC; mucinous, medullary, papillary and tubular cancers. Tubular cancers are by definition of low grade, and correctly classified of having excellent prognosis [10,11].

1.1.4 Estrogen and Progesterone Receptors

Estrogen Receptors (ER) and Progesterone Receptors (PR) belong to the nuclear receptor super family.

The classic mechanism of these receptors is to be activated by ligands (estrogen and progesterone) that bind to the receptor. The ligand-bound receptor then binds another ligand-receptor complex. Together with coactivators, corepressors, and other transcription factors in the cell nucleus this dimer binds to promoter regions of the DNA thereby influencing gene transcription [12]. In normal breast tissue, the concentrations of ERα are low, and expressed in cells in the tubulo-lobular alveolar unit of the breast. The cells expressing ERα almost
never simultaneously express proliferation markers. They are instead expressed in adjacent cells. In premalignant breast tissue, ERα is expressed at higher concentrations in a larger proportion of the cells, and often together with proliferation markers. In BC, 60-80% of tumours express ERα, often at high levels [13]. The proportion of tumours expressing ER increases with increasing age [14]. PRs exist in two variants, PRA and PRB. The two variants come from the same gene, but are regulated by two different estrogen-regulated promoters [15]. In normal breast tissue, PRA and PRB are similarly expressed, while in atypical hyperplasia, non-invasive and invasive BC, PRA and PRB are heterogeneously expressed in adjacent cells, and PRA is often much more expressed than PRB in noninvasive and invasive cancers [16].

Currently, receptor status is assessed with immunohistochemical methods, with at least 10% positive nuclei as a common cutoff [17]. ER and PR are correlated to each other. Absence of PR in Estrogen Receptor Positive (ER+) tumours has been found to be correlated to tamoxifen resistance, and proposed to be an indication of nonfunctioning ER. However, recent data indicate that these tumours are not resistant to aromatase inhibitors, and that absence of PR instead indicates increased growth factor signaling [18,19].

ER and PR are prognostic factors, in that the survival pattern differs between receptor positive and negative tumours [14]. Estrogen Receptor Negative (ER-) and Progesterone Receptor Negative (PR-) tumours have a high mortality peaking around two years after diagnosis, then crossing the receptor positive curves to a much lower mortality rate. On the other hand, ER+ tumours have a rather constant mortality. Consequently, ER+ tumours have a better survival in the first years after diagnosis, but 15 years after diagnosis, the BC survival is unrelated to ER status [6,20]. ER and PR are treatment predictive factors. A majority of tumours expressing ER and PR respond to anti-estrogenic therapy, both in the adjuvant and metastatic setting. ER+PR- tumours respond to tamoxifen, but not as good as ER+/PR+ tumours [21],
and recent data indicate that these tumours are more likely to respond to aromatase inhibitors [18]. ER- tumours do not respond to anti-estrogenic therapy [6] Human Epidermal Growth Factor Receptor 2 (HER2) proto-oncogene encodes a tyrosine kinase situated in the cell membrane. It is over-expressed in approximately 30% of BCs and associated with more aggressive tumour characteristics and poorer survival [5].

1.1.5 Molecular Subtypes

Most studies divide BC into four major molecular subtypes:

- Luminal A
- Luminal B
- Triple negative/basal-like
- HER2 type

Other less common molecular subtypes have also been described including normal breast-like, apocrine molecular type and claudin-low type. BCs that do not fall into any of these subtypes are often listed as unclassified.

At this time, molecular subtypes are used mostly in research settings and are not included in pathology reports. Prognosis and treatment decisions are still guided by tumour stage, hormone receptor status and HER2 status.

The complex profile of each subtype is determined using molecular and genetic information from tumour cells. However, some characteristics (including hormone receptor status, HER2 status and proliferation rate) can be used to roughly define the four major subtypes (Table 1.1). Much of what is known about the four subtypes is related to these characteristics that are already well understood. Most BCs are luminal tumours. Luminal tumour cells look the most like the cells of BCs that start in the inner (luminal) cells lining the mammary ducts.
Table 1.1: Molecular Subtypes of Breast Cancer

<table>
<thead>
<tr>
<th>Subtype</th>
<th>These tumours tend to bea</th>
<th>Prevalence (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER+ and/or PR+, HER2-, low Ki67</td>
<td>40%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>ER+ and/or PR+, HER2+ (or HER2- with high Ki67)</td>
<td>20%</td>
</tr>
<tr>
<td>Triple negative/basal-like</td>
<td>ER-, PR-, HER2-</td>
<td>15-20%</td>
</tr>
<tr>
<td>HER2 type</td>
<td>ER-, PR-, HER2+</td>
<td>10-15%</td>
</tr>
</tbody>
</table>

Abbreviations: ER+ Estrogen Receptor Positive, ER-, Estrogen Receptor Negative; HER2+, Human Epidermal Growth Factor Receptor Positive; HER2-, Human Epidermal Growth Factor Receptor Negative; PR+, Progesterone Receptor Positive; PR- = Progesterone Receptor Negative

aThese are the most common profiles for each subtype. However, not all tumours within each subtype will have all these features.
Adapted from selected sources [22,23].

1.1.5A Luminal A

Luminal A tumours tend to be ER+ and/or Progesterone Receptor Positive (PR+), Human Epidermal Growth Factor Receptor 2 Negative (HER2-) and are tumour grade 1 or 2. Fewer than 15% of luminal A tumours have p53 mutations, a factor linked with poorer prognosis [22].

Of the four subtypes, luminal A tumours tend to have the best prognosis, with fairly high survival rates and fairly low recurrence rates [23,24]. Because luminal A tumours tend to be ER+, treatment for these tumours often includes hormone therapy.

1.1.5B Luminal B

Luminal B tumours tend to be either ER+ and/or PR+. They are highly positive for Ki67 (have a high number of cancer cells actively dividing) and/or Human Epidermal Growth Factor Receptor Positive (HER2+)

Women with luminal B tumours are often diagnosed at a younger age than those with luminal A tumours [25] and, compared to luminal A tumours, they tend to have factors that lead to a poorer prognosis including [26] poorer tumour grade, larger tumour size, lymph node-positive...
and p53 gene mutations (about 30%). In some studies, women with luminal B tumours have fairly high survival rates, although not as high as those with luminal A tumours [22,24].

**1.1.5C Triple negative/basal-like**

Triple negative breast cancers (TNBC) are ER-, PR-, HER2-. There are several subsets of TNBC. One subset is referred to as basal-like because the tumours have cells with features similar to those of the outer (basal) cells surrounding the mammary ducts. Most basal-like tumours contain p53 mutations [22].

Most triple negative tumours are basal-like and most basal-like tumours are triple negative. However, not all triple negative tumours are basal-like and not all basal-like tumours are triple negative. About 15-20% of breast cancers are triple negative or basal-like [22,23]. These tumours tend to occur more often in younger women and African-American women [22,25,27,28]. And, most Breast Cancer 1, Early Onset (BRCA1) BCs are both triple negative and basal-like [27,29,30]. Triple negative/basal-like tumours are often aggressive and have a poorer prognosis (at least within the first five years after diagnosis) compared to the ER+ subtypes (luminal A and luminal B tumours) [31].

**1.1.5D HER2 type**

The molecular subtype HER2 is not the same as HER2+ and is not used to guide treatment. Although most HER2 type tumors are HER2+ (and named for this reason), about 30% are HER2-. HER2 type tumors tend to be ER-, PR-, Lymph node-positive and poorer tumour grade [24,32].

About 10-15% of BCs have this molecular profile [22,23]. About 75% of HER2 type tumours contain p53 mutations [32].

HER2 type tumours have a fairly poor prognosis and are prone to early and frequent recurrence and metastases [28,33,34]. Women with HER2 type tumours appear to be diagnosed at a younger age than those with luminal A and luminal B tumours [23].
1.2 Descriptive Epidemiology

Every day, thousands of women around the world from all walks of life are diagnosed with BC. It is by far the most common cancer amongst females worldwide with nearly one million new cases each year, representing one in five of all female tumours. Overall BC accounts for 21% of all cancer diagnoses in women. BC is the most common cancer in women in high-, middle- and low-income countries [35].

1.2.1 Burden of Disease

Worldwide 1,676,633 women were diagnosed with BC. The burden of BC is higher in less developed regions with 882, 949 cases than in more developed regions with 793, 684 cases estimated by Globocan, 2012. India itself has burden 144,937 BC cases. This implies that, though, the percentage of total women affected seems less, the BC burden in India has almost reached about 2/3rds of some of the developed nations and is steadily rising [36].

1.2.2 Incidence

BC incidence is fast increasing in economically transiting countries though incidence rates in high income countries are nearly three times higher than in middle- to low-income countries. Around the world, age adjusted incidence rates range from 75-100 per 100, 000 women in North America, Northern Europe, and Australia, to less than 20 per 100, 000 in parts of Africa and Asia [37] (Figure 1.2). The adaptation of a western lifestyle – an increased prevalence of ill-defined series of reproductive, hormonal and dietary determinants in the population – has been postulated as a primary reason for the increasing BC incidence rates observed among Asian and Asian American women [38].
1.2.3 Survival

The 5-year survival for female BC is higher than for most other types of cancer. Five year survival ranges from 90 to less than 50%, depending on the characteristics of the tumour, its size and spread, and the availability of treatment [39]. A considerable difference has also been reported in average 5-year survival in low to middle income countries having less than 60% in Brazil and Slovakia and less than 40% in Algeria as compared to high income countries having average 5-year survival proportion of more than 80% in North America, Sweden, Japan, Finland and Australia [39]. The low survival at the end of 5 years in middle- and low-income countries can be explained mainly by a lack of early detection programmes, resulting in a high proportion of women presenting with late-stage disease, as well as by a lack of adequate diagnosis and treatment facilities [40–43]. Educational and cultural barriers also exist for women in less developed countries which often lead to late presentation, such as lack
of awareness of BC, an incorrect belief that the disease is incurable or contagious, the stigma of having a mastectomy and fear of rejection by their partner or community [44,45].

1.2.4 Mortality

The World Health Organization (WHO) has estimated that female BC resulted in a total of 5,884,000 years of life lost globally during 2004. This represented just over 1% of all premature mortality amongst females, but there was a large amount of variation in this proportion between regions, ranging from around 8% in parts of Europe to less than 0.5% in Africa [46]. There is a three-fold variation in mortality by regions of the world, with rates in excess of 20 deaths per 100,000 in Southern Africa, Western Africa and Northern Europe in contrast to 7 to 9.4 deaths per 100,000 in Eastern and Southern Asia [37,47] (Figure 1.3). Rapid increases in mortality have been reported in parts of Asia, Africa and Central/South America [48,49], which have been attributed to rising incidence in conjunction with lower survival. This contrasts with widespread decreasing trends in BC mortality rates of between 2.0% and 3.0% per year throughout North America, parts of Europe and Australia that generally commenced around the late 1980s/early 1990s [50,51].

Figure 1.3: Age Standardized (world) Mortality Rate (per 100,000) of Female Breast Cancer (All ages).
1.2.5 Time trends in Incidence

The most recent incidence data indicate signs of a plateau in time trends in developed world during the mid-1990s, particularly in the Netherlands, Sweden and in England and Wales [52]. Differential trends among pre- and postmenopausal women has been observed in many European countries, where the increases in incidence were observed to be relatively minor in 35–49 years old women but greater in women 50–69 years old. In the U.S. and Canada, BC incidence among postmenopausal women increased in the 1980s and 1990s, stabilized in the late 1990s [53] and declined around 2003 [54], most likely due to saturation of mammography screening [55].

In economically-transiting countries like India and China, incidence rates are increasing, and are predicted to increase further in the next few decades [56,57]. Most registries in India have exhibited rising incidence rates of BC in recent years [58]. As an example, reproductive lifestyle factors appear to be changing in India, with the percentage of women married by the age of 18 declining from 54.2% in 1992-93 to 44.5% in 2005-06. Similarly parity has reduced from 3.39 live-born children per woman delivered in 1992-93 to 2.68 by 2005-06. The use of contraceptive pill has increased from 1.2% to 3.1% [59]. Further the observations may also be explained by differences in the prevalence of specific risk factors in India that increase the risk of pre- or postmenopausal BC, such as obesity [60,61].

1.2.6 Incidence rates in Rural and Urban India

The rates are fast increasing in developing countries like India [62]. However, there are substantial differences in the incidence rates of BC within rural and urban areas of India. Rates observed in metro registries are in the range of 29 – 35 per 100,000 whereas those observed in rural registries vary from 11 -12 per 100,000 [58]. The lowest BC incidence rates are found among women from the rural area of Barshi in Western India, and Dindigul Amblikkai, another rural area in the more developed South of India (Table 1.2). An increasing
order of rate ratio was observed in the present study from rural to urban to metro regions, clearly suggesting the underlying differences in the incidence rates between rural and urban regions (Table 1.3). A twofold increased risk was observed in urban areas and a threefold increased risk was observed in metro areas compared to rural areas [63]. The cause of this strong urban: rural difference is not known although it is likely to be due to one or more lifestyle factors whose prevalence differs strongly between rural and urban women.

Table 1.2: Breast Cancer incidence in South Asian and Western Population (AAR)

<table>
<thead>
<tr>
<th>Rural Population</th>
<th>Town/Small City Population&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Urban Population&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Western Population&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barshi Rural (12.30)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Barshi Town (14.40)</td>
<td>Bangalore (36.60)</td>
<td>US - SEER 9 White (91.8)</td>
</tr>
<tr>
<td>Ahmedabad – rural (11.10)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Aurangabad (18.80)</td>
<td>Bhopal (27.40)</td>
<td>UK, England Thames (82.6)</td>
</tr>
<tr>
<td>Dindigul Amblikkai (13.80)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Chennai (32.60)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mumbai (31.00)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AAR, Age Adjusted Incidence Rate (world) per 100,000 population
<sup>a</sup>NCRP (2009 – 2011)
<sup>b</sup>Cancer Incidence in five Continents Vol X (2003 – 2007)
<sup>c</sup>Personal Communication
Table 1.3: Incidence rate and Rate ratio of developing Breast Cancer in selected cancer registries stratified by Rural, Urban, and Metro regions

<table>
<thead>
<tr>
<th>Regions</th>
<th>Indian registry</th>
<th>Year</th>
<th>AAR</th>
<th>Rate Ratio</th>
<th>95% CI</th>
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</thead>
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<tr>
<td><strong>Rural</strong></td>
<td>Barshi</td>
<td>2009-2010</td>
<td>12.30</td>
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<td></td>
<td>Ahmedabad rural</td>
<td>2009-2010</td>
<td>11.08</td>
<td>0.90</td>
<td>0.64-1.26</td>
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<tr>
<td><strong>Urban</strong></td>
<td>Aurangabad</td>
<td>2009-2010</td>
<td>18.78</td>
<td>1.53</td>
<td>1.13-2.06</td>
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<tr>
<td></td>
<td>Bhopal</td>
<td>2009-2010</td>
<td>27.39</td>
<td>2.23</td>
<td>1.76-2.82</td>
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<tr>
<td></td>
<td>Wardha</td>
<td>2010-2011</td>
<td>18.26</td>
<td>1.48</td>
<td>1.11-1.98</td>
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<td><strong>Metro</strong></td>
<td>Bangalore</td>
<td>2008-2009</td>
<td>36.65</td>
<td>2.98</td>
<td>2.51-3.54</td>
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<td></td>
<td>Chennai</td>
<td>2009</td>
<td>32.63</td>
<td>2.65</td>
<td>2.17-3.25</td>
</tr>
<tr>
<td></td>
<td>Mumbai</td>
<td>2008-2009</td>
<td>30.97</td>
<td>2.52</td>
<td>2.10-3.01</td>
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<td></td>
<td>Nagpur</td>
<td>2009-2010</td>
<td>32.46</td>
<td>2.64</td>
<td>2.15-3.24</td>
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<td></td>
<td>Pune</td>
<td>2009-2010</td>
<td>23.27</td>
<td>1.89</td>
<td>1.52-2.36</td>
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<td></td>
<td>Thiruvananthapuram</td>
<td>2009-2011</td>
<td>35.07</td>
<td>2.85</td>
<td>2.34-3.47</td>
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<td><strong>North East</strong></td>
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<td>2009-2010</td>
<td>30.33</td>
<td>2.47</td>
<td>1.67-3.64</td>
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<td>regions</td>
<td>Cachar District</td>
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<td>16.44</td>
<td>1.34</td>
<td>1.00-1.78</td>
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<td>Dibrugarh District</td>
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<td>10.63</td>
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<td>East Khasi Hills</td>
<td>2010-2011</td>
<td>12.10</td>
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<td>Imphal West District</td>
<td>2009-2010</td>
<td>14.36</td>
<td>1.17</td>
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<td></td>
<td>Manipur (excluding</td>
<td>2009-2010</td>
<td>7.59</td>
<td>0.62</td>
<td>0.42-0.91</td>
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<td></td>
<td>Imphal West)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kamrup Urban District</td>
<td>2009-2011</td>
<td>22.76</td>
<td>1.85</td>
<td>1.43-2.39</td>
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<td></td>
<td>Manipur</td>
<td>2009-2010</td>
<td>9.14</td>
<td>0.74</td>
<td>0.52-1.06</td>
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<td>Meghalaya</td>
<td>2010-2011</td>
<td>9.10</td>
<td>0.74</td>
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<td></td>
<td>Mizoram</td>
<td>2009-2010</td>
<td>16.40</td>
<td>1.33</td>
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<td>Mizoram (excluding</td>
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<td>8.54</td>
<td>0.69</td>
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<td>Aizawl)</td>
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<td></td>
<td>Nagaland</td>
<td>2010</td>
<td>9.52</td>
<td>0.77</td>
<td>0.42-1.43</td>
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<td>Sikkim</td>
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<td>8.56</td>
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<td>Tripura</td>
<td>2010</td>
<td>7.16</td>
<td>0.58</td>
<td>0.39-0.87</td>
</tr>
</tbody>
</table>

Abbreviations: AAR, Age adjusted incidence rate (world) per 100,000; CI, Confidence interval; NCRP, National Cancer Registry Program.
1.3 Etiology

1.3.1 Reproductive Factors

Some reproductive factors modify sex hormone levels; reduction in overall estrogen exposure may partly explain the link between reproductive factors and BC risk.

1.3.1A Age at Menarche and Menopause

Menarche and menopause are markers of onset and cessation, respectively, of ovarian and related endocrine activity associated with reproduction. During women's reproductive years (broadly the time between menarche and menopause) the ovary produces steroid hormones that directly affect development and function of the breast. Early menarche and late menopause are known to increase women's risk of developing BC. BC risk increases by 5% for each year younger at menarche and a 3% increase has been observed for each year increase in menopause, a meta-analysis has shown [64]. Most of the cohort studies have shown direct relation between age at menopause and BC risk [65–69].

An early age at menarche is thought to be associated with an increased risk of BC because a higher number of lifetime ovulatory cycles, and hence greater exposure to ovarian hormones, has been shown to confer an elevated risk of BC [65]. The association between age at menarche and BC is stronger for ER+ and PR+ tumours than for ER- and PR- tumours [70].

1.3.1B Age at first full-term birth and Parity

Compared to nulliparous women, mothers with their first full-term birth before 20 years of age had a 50% reduced risk of BC. On the other hand, those who had their first baby after age 35 had a 22% increased risk. BC risk decreases by 7% with each live birth [70–73] and increases by 3% for each year older a woman is when she first gives birth, meta- and pooled analyses have shown [71]. These relative risk (RR)s were comparable across countries. The protective effect of early age of first full-term birth in parous women was similarly observed
in other studies [74] except for one study from Japan [75]. The association of age at first full-term pregnancy has been found to be similarly associated with pre- and postmenopausal women [76,77]. Many reports observed a protective effect of early age at first full-term birth on Hormone Receptor Positive (HR+) cancers [34,78,79]. A meta-analysis has also revealed a reduced risk among patients with HR+ cancers [70]. When stratified on receptor status, the association between parity and age at first full-term birth and BC risk however was shown to be limited to ER+/PR+ tumours [34,70,80].

1.3.1C Interval between age at menarche and age at first full-term pregnancy

Given the susceptibility of the undifferentiated nulligravid breast to carcinogenic insults, the duration of time between age at menarche and age at first full-term birth may be independently related to BC risk. However, few epidemiologic studies have evaluated this relation. Clavel-Chapelon [65] addressed this issue to some extent in the French E3N cohort by evaluating the relation between the number of menstrual cycles women had before their first full-term birth and BC risk. Compared with women in the lowest quartile, women in the highest quartile of cumulative number of cycles before their first full-term birth had a 1.42-fold [95% Confidence Interval (CI): 1.20–1.67] elevated risk of BC. This risk was essentially the same when women who had used Oral Contraceptives (OC)s were excluded from the analysis. In a combined analysis of 7 case-control studies, Andrieu et al. found similar results. BC risk for women with 21 or more years between menarche and first childbirth was 1.45-fold higher (95% CI: 1.17–1.82) than that for women with 10 years or less between these two events [81]. A longer duration between age at menarche and age at first full-term birth was associated with an elevated risk of BC, except among premenopausal African-American women. The elevations in risk observed were largely confined to women with HR+ tumours [82]. The large body of data indicates that the risk of BC overall increases with the increase in interval between age at menarche and age at first full-term pregnancy.
1.3.1D Breastfeeding

Breastfeeding has been hypothesized to reduce the risk of BC. However, findings haven’t been consistent for the association between BC risk and ever breastfeeding or cumulative breastfeeding duration [83,84]. However, a reduction has been seen most consistently observed among premenopausal women who breastfed for an extended period, but even here the magnitude of the observed effect has varied substantially [83]. Breastfeeding appears to lower the risk of both ER+ and PR- BCs [70]. A pooled analysis from 47 epidemiologic studies, including 50,302 cases and 96,973 controls, showed a significant, 4.3% reduction in BC risk for every 12 months of breastfeeding [71]. A systematic review carried out by Berrino et al. for the World Cancer Research Fund/ American Institute for Cancer Research (WCRF/AICR) included 80 epidemiologic studies. The meta-analysis on four cohort studies as well as that on 37 case-control studies showed a 2% reduction of risk per 5 months of breastfeeding [85]. In a systematic review on Japanese population, cohort studies failed to find a significant inverse association between breastfeeding and the risk of BC and most of the case-control studies observed a statistically significant or non-significant risk reduction for women who ever had breastfed or for women with a longer duration of breastfeeding [86]. In a case-control study conducted in India, where longer duration of breastfeeding is more common as compared to the western population showed an inverse association with BC in premenopausal women, whereas no such protective effect was observed in postmenopausal women [87]. The current literature indicates a weak protection in the development of BC in women who have breast fed for a longer duration.

1.3.1E Induced and Spontaneous Abortions

The relationship between induced abortion and the subsequent development of BC has been the subject of a substantial amount of debate in epidemiologic studies. In contrast to a recent
meta-analysis conducted in Chinese women [88] which largely included retrospective studies (34 case-control studies and 2 cohort studies), prospective studies conclude there is no association between induced abortion and BC [89–95]. A worldwide meta-analysis of 83,000 women examined the relationship between induced abortion and BC and found a significant difference between the overall estimate of RR from studies that had recorded information on induced abortion prospectively (RR = 0.93; 95% CI: 0.89–0.96) and the overall estimate of RR from studies that had recorded such information retrospectively (RR = 1.11; 95% CI: 1.09–1.14), suggesting that reporting bias was probably present in studies using retrospective reporting of abortion history [96]. Findings from cohort studies and a large pooled analysis have shown spontaneous abortion (also known as miscarriage) does not increase the risk of BC [90,93,94,96]. On the other hand premenopausal BC appeared to be less frequent in women who had repeated miscarriages suggesting BC association with spontaneous abortion is possible and may depend on menopausal status [97]. The current literature is divided on the association of spontaneous abortion and BC risk, whereas the results are inconclusive for the association of induced abortion with BC risk

1.3.1F Oral Contraceptives

Studies show that current or recent use of OCs (birth control pills) slightly increases the risk of BC [98–100]. The Women’s CARE Study examined the risk of BC associated with OCs among different subgroups of women. In this study, there was no increased risk of BC among current users (RR = 1.0, 95% CI: 0.8–1.0) or former users (RR = 0.9, 95% CI: 0.8–1.0). This study found no increased risk among women with a family history or those who initiated use at an early age. In addition, the risk of BC did not appear to vary by duration, dose or type of progestin [101]. Similarly, a recent systematic review showed that, the RR of BC declines after OC cessation, such that 10 years after cessation no excess risk remains. BC risk does not
appear to increase with longer duration of OC use [102]. A meta-analysis has shown that the risk associated with OC is similar across OC formulations (which have changed considerably over time), family history, and ethnicity [103].

Studies that evaluated the risk by ethnicity observed effect estimates greater for black women [101,104] than for white women [105]. In a follow-up study of Norwegian women, the RR estimate was 1.6 (95% CI: 1.2–2.1) for women who were current or recent OC users at baseline [99]. Another follow-up study in the Netherlands, showed long duration OC use was associated with increased BC risk among women aged 55 years or older but not younger women [106]. In a Long Island case-control study of BC, recent OC use and long duration OC use were associated with increased BC risk among premenopausal women but not among postmenopausal women [107]. In the population based Carolina BC Study, results were close to the null for white women, but OC use within the previous 5 years was associated with increased risk among black women [104]. With regard to the hormone status of the tumour, some studies have found stronger associations of OC use with ER- cancer than with ER+ cancer [108,109], but others have found no difference [110–114]. The current literature suggests that OC use increases the risk of BC in current long term users.

1.3.1G Non-oral hormonal contraceptives

Hormonal contraception is also available as injections, implants and patches. There is substantially less evidence on cancer risk associated with these preparations than there is on cancer risk associated with the OCs. BC risk is increased among users of injectable contraceptives in some studies [111,112], while other study showed no association [113]. In a case-control study a significantly increased association between BC risk and implants was observed [115]. The literature for the association non-oral hormonal contraceptives with BC risk is inconsistent and more studies with larger sample size will be required to estimate a true association.
1.3.1H Tubal Ligation

The US Collaborative Review of Sterilization reported reduced menstrual bleeding and pain and increased cycle irregularity after tubal ligation [116]. These findings provided evidence against a ‘post tubal ligation syndrome’ that included dysmenorrhoea and menorrhagia, but could not address long term outcomes, such as altered menopausal age [117], symptoms [118–120], or BC risk. A recent meta-analysis reported no association between tubal ligation and BC, however, substantial heterogeneity was observed. Effect estimates among eight studies ranged from 0.37 (95% CI: 0.19–0.68) to 1.20 (95% CI: 1.00–1.30) [121]. This variability may be partly due to incomplete information on subsequent gynaecologic surgeries and tumour subtypes. Few studies have evaluated variation by tumours that express ER or PR and may therefore be more sensitive to hormonal exposures [122,123]. Similarly, in a recently conducted case-control study, tubal ligation did not have an impact on BC overall (Hazards Ratio = 0.95; 95% CI: 0.85–1.06), but had a suggested inverse relation with ER+/PR+ invasive tumours (Hazards Ratio = 0.84; 95% CI: 0.70–1.01), possibly because of subsequent hysterectomy/bilateral oophorectomy [124]. The current literature does not show any association of tubal ligation with BC risk.

1.3.1I Age at last full-term pregnancy

Age at last full-term pregnancy did not show an association [Odds Ratio (OR) = 1.01; 95% CI: 0.97–1.06] with BC [125].

In European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, age at last full-term pregnancy was not associated with the risk of ER-/PR- malignancies but was associated with ER+/PR+ tumours, however no statistical heterogeneity between the BC subtypes was observed [80].
1.3.1J Twin Pregnancy

Twin pregnancies differ from singleton pregnancies in both hormone levels and perinatal changes [73]. Some studies have suggested that twin births may be associated with lower BC risk [126,127]. Although in pooled results of all 17 published studies did not show a reduced maternal risk of BC for twin births (Hazards Ratio = 0.94; 95% CI: 0.87–1.02; \( P = 0.127 \)), a trend toward reduced maternal risk of BC was identified in a subgroup analysis of cohort studies (Hazards Ratio = 0.91; 95% CI: 0.83–1.01; \( P = 0.068 \)). The results of the only meta-analysis suggest that twin pregnancy does not significantly decrease the maternal risk of BC [73]. The current literature is inconclusive on the relationship between twin pregnancies and risk of BC.

1.3.1K Duration since last birth

Liu et al. [128] from the Swedish Fertility Register, with over 30,000 BC case subjects available for study documented a small increase in the risk of BC for each of the first few years after birth, with adjustment for age at delivery in 1-year increments. Other studies, with considerably smaller numbers of white women, have produced mixed results: some observed an increased risk for shorter interval since last birth [129–131] and a few found no association [132–134]. Duration since last birth has been shown to be associated with ER+/PR+ tumours and not with ER-/PR- tumours [80].

1.3.2 Anthropometric Measurements

1.3.2A Height

Height, representing intrauterine, early childhood as well as the level of adolescent growth spurt, likely relates to factors such as nutrition, genetic growth potential, and hormones thus influencing BC occurrence [135–138]. A positive association between adult height and BC has been found in a large number of studies [61,135,139,140]. In a review of seven large prospective cohort studies, the multivariate-adjusted RR of BC per 5 cm increment of height
was 1.02 (95% CI: 0.96–1.10) in premenopausal women and 1.07 (95% CI: 1.03–1.12) among women of postmenopausal status [139]. A meta-analysis conducted on premenopausal women found an overall weak association with each increment of 10cm in height [141]. Another study showed a positive association of BC risk with postmenopausal women [142]. However some studies have found no association at all with height in pre- or postmenopausal women of European descent [143]. Previous studies have generally not shown any clear differences for overall height associations by ER/PR status of the BC cases [144–148].

Previous studies have consistently associated tallness with increased risk of BC overall.

1.3.2B Body Mass Index (BMI)

Most available studies and meta-analyses have focused on BMI as a marker of general obesity [112,139,149–153]. Several studies supported the hypothesis that higher level of BMI may be associated with a decrease in the risk of premenopausal BC. This hypothesis is supported by results from several case-control studies [109,143,154,155] and cohort studies [156,157]. However, others studies did not observe a statistically significant association when comparing highest versus lowest levels of BMI [61,158,159]. Ethnicity appears to modify this association because while the inverse association between BMI and risk of premenopausal BC is well documented in Caucasians, the association among Asian women is inconsistent. Several studies among Asian women suggest that higher BMI may be associated with an increased risk of premenopausal BC [149,150,160,161]. A prospective study including 11,889 women from Taiwan reported that higher BMI was moderately associated with an increased risk of premenopausal BC [161], with an OR of 1.90 (95% CI: 1.00–3.4) for BMI > 26.2kg/m² versus 21.6kg/m². In contrast, other studies among Asian women did not detect a significant association between BMI and the risk of premenopausal BC [162,163]. In a recent meta-analysis it has been shown that premenopausal BMI does not relate to BC risk [164].
An overall increase in the risk of postmenopausal BC in overweight or obese women among all ethnic groups has been indicated. The association between BMI and risk of postmenopausal BC was found to be stronger among women who did not use hormone replacement therapy (HRT) compared to women who did use hormones [165]. A dose-response meta-analysis (9 cohorts: 22 case-control studies) showed that the BMI-BC association is stronger for ER+/PR+ tumours (33% increase per 5kg/m² increment for postmenopausal BC), while there were no significant BMI-cancer associations for ER-/PR-tumours [166].

1.3.2C Waist-to-Hip ratio (WHR)

WHR is commonly used as a measure of central obesity [167,168]. It has not been consistently associated with increased BC risk in premenopausal women, for whom both null [61,155] and increased risk have been reported [143,167–169]. Two meta-analyses [168,169] have reported that a greater WHR was associated with about 1.5-fold increased risk of premenopausal BC. A pooled analysis on 7 cohorts and 4 case-control studies reported a summary risk estimate of 1.79 (95% CI: 1.22–2.62) [169] but the strength of the association varied according to ethnic groups [170–173]. Other studies [146,161,174] did not find a statistically significant association. Overall, this increased risk associated with larger WHR among premenopausal women is found to be stronger amongst Asian women compared to other ethnic groups.

A WHR of above 0.85 for females has often been associated with the risk of developing postmenopausal BC. However, while most studies have reported a significant increased risk [155,169,175], some studies are inconclusive [61,143,156]. A meta-analysis with 6 case-control and 5 cohort studies observed a summary risk estimate of 1.50 (95% CI: 1.10–2.04) for postmenopausal women [169]. These associations tend to be stronger in Asian women than other ethnic groups. In contrast, some studies conducted in the US did not detect a
significant association. Hall et al. reported a non increased RR of 1.62 (95% CI: 0.70–3.79) in African-American women and of 1.64 (95% CI: 0.88–3.07) for Caucasian American women when comparing highest versus lowest quintiles (0.86–1.34 versus 0.6–0.77) [143]. However the power of the study was limited by small number of cases (179 cases and 182 controls in African women). Regarding Hispanic women, only one study has assessed the association between WHR and BC risk. This study found no significant association between WHR and postmenopausal BC risk [176]. Current literature largely suggests that a high WHR is associated with increased risk of premenopausal and postmenopausal BCs.

1.3.2D Waist Circumference (WC)

Among premenopausal women, WC is generally not related to risk of BC in most studies but positive associations have been found when adjusted for BMI [165]. Recent results from the Nurses’ Health Study II showed a strong increase in the risk of ER- BC among premenopausal women with increasing WC (RR = 2.75; 95% CI: 1.15–6.54) [167]. In postmenopausal women, studies that did not adjust for BMI showed a 7% increased risk per 8cm increase in WC and those that did, showed a 4% increased risk [85]. In the Women’s Health Initiative (WHI) study, WC was associated with BC risk among postmenopausal women, but only in those who never used HRT [177].

1.3.2E Hip Circumference (HC)

An inverse association in premenopausal women with HC adjusted for BMI was found in some studies [61,178]. An inverse association was also observed in Nigerian BC Study with an OR of 0.36 for the highest quartile (95% CI: 0.24–0.55). The association existed in both pre- and postmenopausal women [179]. In contrast, other studies showed a positive association between HC and BC risk [177,180]. Again, In WHI, HC was positively associated with both ER+/PR+ and ER-/PR- subtypes of premenopausal BC [181]. The evidence of the association between HC and BC risk has been largely inconsistent [61,177–181].
1.3.2F Adult Body Weight

A number of epidemiological studies have reported that both early adult body weight [157,182,183] and a subsequent change in body weight [157,183–185] are associated with BC risk. Several of these have reported an inverse association between body weight in early adulthood and the incidence of BC [183,185].

It has been postulated that the association between body weight and BC risk may be heterogeneous according to the tumour’s ER and PR status. Cumulative epidemiological evidence [139,186,187] also suggests that the impact of body weight on BC risk differs across women’s menopausal status. Recent meta-analysis of cohort and case-control studies could clarify that overweight is not significantly related to risk of premenopausal BCs [164]. A positive association among postmenopausal women has been observed. Large weight gain since age 20 has been shown to be associated with increased risk of BC [149,188], particularly in postmenopausal women aged >60 years [189–191]. Any weight change since the age of 18 seems not to be related to premenopausal BCs [192]. A large body of data suggests that early adult body weight and a subsequent change in body weight are associated with BC risk.

1.3.3 Other Factors

1.3.3A Physical Activity

Physical activity is a modifiable factor that is associated with a decreased risk for both premenopausal and postmenopausal BC [193,194].

BC risk is around 25% lower in the most active women compared with the least [195]. BC risk decreases by 5% for every 2 hours per week increment in recreational activity (moderate and vigorous), a meta-analysis showed [196]. Light intensity activity may be insufficient to reduce BC risk, a Canadian case-control study indicated [197]. Further BC risk declined with increasing time spent on household activities, a factor which is more prevalent in rural women.
as compared to urban women [198]. Thus it can be concluded that there is sufficient evidence for the role of physical activity in preventing BC [199].

1.3.3B Occupation
Villeneuve et al. [200] in a case-control study (1230 cases) observed a statistically significant BC excess after 10 years duration in motor vehicle manufacturing (obs/exp= 18/7=2.6 (95% CI: 1.00–6.30). Labrèche et al. [201] found significant excesses of postmenopausal cancer for polycyclic aromatic hydrocarbons (PAHs), and several polymeric fibers. Clapp et al found risk was elevated among postmenopausal women whose husbands used specific pesticides [202]. A recent study found that young women exposed to DDT before the age of 14 had an excess BC risk before age 50 [203]. Band et al. [204] found in pre- and postmenopausal cases (combined) elevated BC risk in fruit and other vegetable farming (OR = 3.11, 90% CI: 1.24–7.81).

In meta-analysis of 13 observational studies found a 48% (RR = 1.48; 95% CI: 1.36–1.61) increased risk of BC among shift workers [205]. Exposure to light at night is associated with higher levels of sex hormones, because it disturbs the circadian system, which suppresses melatonin production, and melatonin is thought to reduce circulating estrogen [206,207]. This may partly explain the link between shift work and BC risk, but confounding by other lifestyle factors such as tobacco use, BMI and physical activity is possible [208,209].

1.3.3C Ionizing Radiation
Exposure to ionizing radiation is a well established cause of somatic DNA mutations. BC risk is increased after several types of previous cancer, with radiotherapy an important factor in this association. BC risk is nonsignificantly increased in survivors of childhood solid cancer who received radiotherapy, compared with those who did not receive radiotherapy [210]. BC risk is 9-11% higher in women who received radiotherapy for cancer in the opposite breast, compared with women who had surgery [211,212].
Diagnostic radiology involves much lower radiation doses than radiotherapy. An estimated 0.1% of BC in women aged 75 and under are caused by exposure to diagnostic x-rays [213]. X-ray-associated BC risk is further elevated in women with BRCA1 or Breast Cancer 2, Early Onset (BRCA2) mutation [214]. Mammograms are associated with a very small number of BC: of 10,000 women who are screened every three years between the ages of 47 and 73, between three and six will develop cancer during their lifetime because of mammogram radiation [215]. Exposure to computed tomography (CT) scans in childhood or adolescence does not appear to be linked with increased BC risk [216]. The ionizing radiation thus has been consistently associated with increased risk of BC.

1.3.3D Diet

BC risk decreases with higher consumption of fruit and vegetables [217], dietary fibre (at least 25g/per day) [218], some carotenoids [219], lignans (postmenopausal women) [220], soya-based foods (Asian populations only) [221,222], flavonols and flavones (postmenopausal women) [223], and marine omega-3 polyunsaturated fatty acids (PUFA) [224]. BC risk is not associated with consumption of red meat [225,226], green or black tea [227], use of vitamin supplements [228], or vitamin D levels [229]. BC risk may be slightly increased with higher consumption of eggs, but no dose-response has been shown and confounding may be likely [230]. There was no evidence of an association between traditional dietary patterns and risk of BC [231], and only one study showed a significant increase in risk associated with the western dietary pattern [232]. Diets that include alcoholic beverages may be associated with increased risk [231]. Though links between BC risk and diet have been extensively studied, WCRF/IARC deems the evidence insufficient (due to quality, consistency and amount) to derive classifications as to the breast carcinogenicity of any dietary exposure except total dietary fat [85].
1.3.3E Family history and genetic factors

BC risk is around doubled in women with one first degree relative with BC, compared with women with no first degree relatives, meta- and pooled analyses have shown. The risk is further increased with a larger number of affected first degree relatives, or relatives affected aged under 50 [233]. The risk increase is similar for first degree relatives with ER+ or ER-BC [234].

Environmental and lifestyle factors explain around three-quarters of BC risk, with hereditary factors explaining only around a quarter [235]. The reasons for BC clustering in families remain largely unclear, but a small proportion of families share BC predisposition genes, some of which are discussed below.

High Penetrance Gene Mutations

BRCA1 and BRCA2 mutations confer a high risk of BC in carriers (high penetrance). Women with a BRCA1 or BRCA2 mutation have a 45-65% chance of developing BC by age 70 [236]. BRCA2 negative women with a BRCA2 carrying first degree relative may also have increased BC risk, a small UK cohort study showed [237]. Higher sex hormone levels in BRCA mutation carriers may explain some of the increased risk [238]. Early onset BC risk may be increased in BRCA mutation carriers born in the 1950s or later, suggesting possible interactions with lifestyle factors [239].

Other breast cancer predisposition genes

Li Fraumeni syndrome caused by Tumour Protein 53 (TP53) mutation and Cowden syndrome caused by Phosphatase and Tensin Homolog (PTEN) mutation are high-penetrance BC predisposition genes, but they are both rare and so account for a very low proportion of BC cases overall and among cases with first degree family history. Mutations in Checkpoint Kinase 2 (CHEK2), Ataxia Telangiectasia Mutated (ATM), BRCA1 interacting protein C-
terminal helicase 1 (BRIP1), and Partner and Localizer of BRCA2 (PALB2) confer an intermediate risk of BC in carriers, but again are rare. Mutations in a number of other genes are more common but confer a lower risk of BC. BC risk in some other rare genetic mutation syndromes, such as Peutz-Jeghers syndrome caused by Serine/Threonine kinase 11(STK11) mutation, and hereditary diffuse gastric cancer syndrome [caused by cadherin 1, type 1, E-cadherin (epithelial) (CDH1) mutations], remains unclear [240,241].

**Low Penetrance Polymorphisms**

Several common Single Nucleotide Polymorphism (SNP)s associated with BC have been identified primarily through Genome Wide Association Study (GWAS) of very large case-control populations. These alleles occur with high frequency in the general population, although the increased BC risk associated with each is very small relative to the general population risk. GWAS on BC has largely been conducted in most developed countries [242–245] showing low to modest associations between common polymorphisms and BC risk. Susceptibility locus on Estrogen receptor alpha (ESR1) gene – a key mediator of ER in mammary tissue have consistently shown its association with BC [246]. A meta-analysis confirmed the association of polymorphisms rs1219648 (A > G), rs2420946 (C > T), and rs2981582 (C > T) in Fibroblast Growth Factor Receptor 2 (FGFR2) suggesting that FGFR2 is likely an important genetic marker contributing to susceptibility of BC [247].

**1.3.3F Smoking**

Tobacco smoking is classified by IARC as a probable cause of BC, based on limited evidence [248]. Tobacco smoking is associated with higher levels of sex hormones, which may partly explain the link between tobacco and BC risk [249].

BC risk is 12% higher in current smokers, and 9% higher in former smokers, both compared with never smokers, a meta-analysis has shown [250]. BC risk increases with amount, duration, and starting age of smoking [250,251]. The effect of smoking may be limited to
premenopausal BC and non obese women [251,252], and ER+ (not triple negative) BC [149,253].

1.3.3G Alcohol

In 2007, the IARC concluded that there is sufficient evidence that alcohol causes cancer of the female breast [254]. A meta-analysis has shown that even light drinkers (up to one alcoholic drink per day, or around 1.5 units) have a 5% higher BC risk compared with non-drinkers [255]. Studies have consistently demonstrated a linear dose-response relation between alcohol consumption and BC risk, with increases observed to be around 7-12% per unit of alcohol per day [256–258]. Although the exact mechanism for the association between alcohol consumption and BC is not known, one probable explanation would involve alcohol’s effects on circulating estrogen levels. Most large studies have shown a stronger association with ER+ BCs [259–263]. Alcohol intake is thus the dietary factor most consistently associated with BC risk, although the relationship observed has generally been modest.
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1.4 Gaps in Literature

It has been observed for long time that the rates of BC differ in rural and urban areas. However, there are very few studies in literature to address the reasons for the differences in BC rates of rural and urban area. Obesity has been observed to be risk factor for postmenopausal BC. However the contribution of different measures of obesity and their role in pre- and postmenopausal women is still not clear. In Indian context, there are no large studies to address the issue of reproductive factors, obesity, age at last pregnancy, OC use in development of BC. Though there has been large GWAS on BC in most developed countries [242–245] showing low to modest associations between common polymorphisms and BC risk. In India, however, there have been no GWAS and few properly designed retrospective studies with smaller sample size on genetic susceptibility to study this risk [264–267].

The present thesis proposal is designed to understand more clearly the reasons for rural-urban differences, and role of genetic susceptibility in development of BC.

**HYPOTHESIS**

Anthropometric and Lifestyle related variables are the cause of large differences in occurrence of BC in rural and urban areas.

**AIM**

**Primary:** To study role of anthropometric and other lifestyle related variables in causation of BC in rural and urban areas.

**Secondary:** To study role of genetic susceptibility in BC.