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Ethnicity and Breast Cancer Risk: An Indian Perspective

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Published Date: September 25, 2016

ABSTRACT

Breast cancer **(BC)** is the most common cancer in females globally whereas in India BC is the second most common cancer in females. Population based cancer registries in North Eastern **(NE)** region of India show clear heterogeneity in the incidence rates of BC. Clinical and epidemiological studies have shown that anthropogenic measures, female reproductive status, circulatory steroid hormones, hormone receptor status, use of birth control pills, food habits are significantly associated with the increased risk of BC globally along with genetic heterogeneity and epigenetic alternations in females. In the present review we aim to explore various risk factors of BC in Indian females across different ethnic groups. Early onset of menarche, late age of marriage, late age at first full term pregnancy, low parity status, short span of lifetime duration of lactation, late age of menopause are significantly associated with the increased risk of BC in Indian females which strongly follow ethnic variations. Moreover, it has been found that betel nut chewing with or without tobacco, alcohol consumption habit and tobacco smoking are significantly associated

with the increased risk of BC in females from India. Genetic heterogeneity in mutation patterns and/or methylation status of tumour suppressor, DNA repairs mechanism and immune pathway genes have been found to be ethnically variable. Our study has revealed that high prevalence of invasive ductal carcinoma **(IDC)** and hormone receptor negative subtypes of BC in young premenopausal females in NE region of India. Future, studies with large sample size and genome-wide association studies **(GWAS)**, transcriptome profiling and genetic and environmental risk factor analysis in different ethnic groups will give deeper insight into the epidemiology of BC in India.

Keywords: Menarche; Menopause; First full term pregnancy; Lactation; Betel nut chewing; Tobacco smoking; Alcohol consumption; Invasive ductal carcinoma; Triple negative breast cancer; *TP53; XRCC; TNF-α; TGF-β; TLR2; BRCA;1 BRCA2*

INTRODUCTION

Breast cancer **(BC)** is the most common cancer in women worldwide [1]. Epidemiological studies have shown that global burden of BC is expected to cross almost 2 million by the year 2030 [2]. Clinical and epidemiological studies have shown that anthropogenic measures, female reproductive status, circulatory steroid hormones, hormone receptor status, use of birth control pills are significantly associated with the increased risk of BC in females [3]. Moreover, studies have revealed that food habits are also significant effect modifiers in the risk of BC [4]. Molecular epidemiological studies have revealed that genetic and epigenetic alternations are also significantly associated with the risk of BC globally [5]. However, studies have shown that genetic and epigenetic alternations along with putative risk factors in reproductive status and dietary habits associated with BC also vary with ethnicity in different geographical regions [6]. For past two decades ethnic variations in the risk of BC have been studied extensively by several researchers globally [7].

In India, BC is the second most common cancer in females [8]. Population-based cancer registry **(PBCR)** data has shown that in India every year average 80,000 females are diagnosed with BC in which 40,000 die annually [9]. Epidemiological studies have revealed that incidence of BC has emerged as leading cancer in most urban populations in India marked by late marriage, bearing children later in their life and short span of lactation [10]. PBCR data from India have revealed that BC incidence significantly varies with ethnicity and the highest incidence of BC has been reported in North Eastern Region **(NER)** of India (Age Adjusted incidence Rate or AAR per 100,000 population is 19 in Dibrugarh district, Assam, 17.5 in Kamrup district, Assam, 14.5 in Aizawl district, Mizoram) and in major metropolitan cities, like Bangalore (AAR per 100,000 population is 27.5), Mumbai (AAR per 100,000 population is 28.6) and New Delhi (AAR per 100,000 population is 28.6) [11]. Epidemiological studies have revealed that high incidence of BC in India is in premenopausal females [9]. Moreover, epidemiological studies have suggested that socio-demographic factors like reproductive status and lifestyle habits play a crucial role in

the genetic susceptibility to BC in India [12]. PBCR data have suggested that family history of BC is most important factor for the early onset of BC in Indian females [12], whereas reproductive status and lifestyle habits are the crucial factors associated with increased or decreased risk of BC in females from India [13].

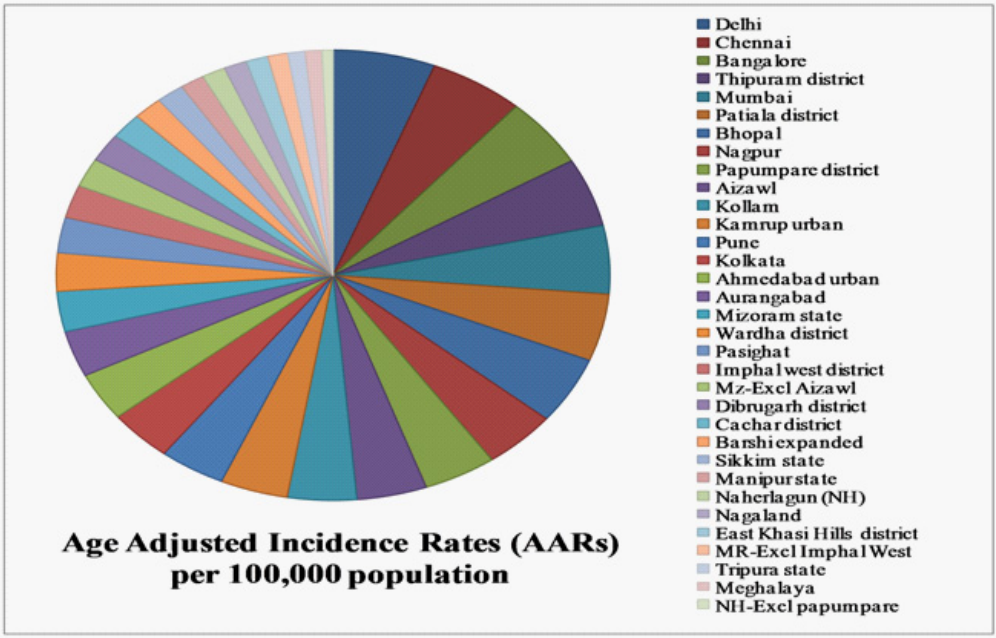

Figure 1: Comparison of Age adjusted Incidence Rates (AARs per 100,000 population) of breast cancer **(BC)** in females of all Population Based Cancer Registries **(PBCRs)**, 2012-2014, published by Indian Council of Medical Research **(ICMR)** on 2016.

CLASSIFICATION OF BREAST CANCER TYPES

Histopathological Classification of BC

Histopathologically BC is classified into two broad categories, namely invasive carcinoma and carcinoma *insitu* [14]. Hospital-based studies have shown that invasive carcinoma is the most prevalent type of BC in India [15]. Pathological studies have revealed that invasive carcinoma of the breast is distinctly divided into further subtypes, like infiltrating, lobular, colloid, tubular, medullary and papillary invasive carcinoma in which infiltrating ductal carcinoma **(IDC)** is most common, accounting for 70-80% of total BC cases globally [15]. Similar to invasive carcinoma of the breast, insitu carcinoma is also subdivided into ductal carcinoma *in situ* **(DCIS)** and lobular carcinoma *in situ* **(LCIS)** subtypes [15]. Clinical studies have revealed that DCIS is more prevalent than LCIS and DCIS type is further subdivided into comedo, cribiform, micropapillary, papillary and solid subtypes of BC [15]. PBCR data have shown that IDC subtype of BC is the most prevalent type of BC in India [16].

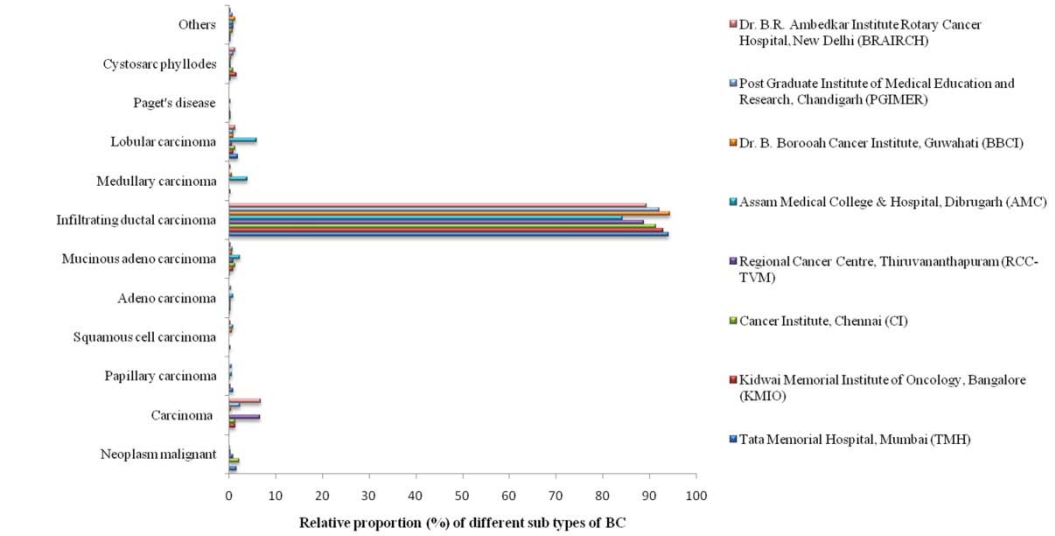

Figure 2: Relative proportion (%) of different histological types of breast cancer **(BC)** in India by consolidated report of the Hospital Based Cancer Registries **(HBCRs)**: 2012-2014, published by Indian Council of Medical Research **(ICMR)** on 2016.

Immunological classification of BC

Current classification of BC is based on the presence of hormone receptors, especially estrogen receptor **(ER)**, progesterone receptor **(PR)** and human epidermal growth factor receptor (Her2) on breast tissue by Immunohistochemistry **(IHC)** and has gained much attention [15]. ER and PR are nuclear receptors, present on breast epithelial cells to regulate breast development by endocrine stimuli during puberty and pregnancy [17]. The presence or absence of ER, PR and Her2/neu is considered to be crucial for the determination of BC prognosis and therapeutic decision making [18]. Clinical studies have shown that ER+ BC subtypes can be treated with specific endocrine therapies more effectively than ER- subtype [19] whereas studies have shown that Her2 status could antagonize the expression of ER and PR as evidenced in several BC tissue samples where high expression of Her2 have been found to inhibit the expression of PR status [20]. PBCR data from India have shown that ER+/ PR+ tumours include 20-45% of total BC cases for which hormone receptor status was tested in which almost 50% patients exhibit Her2 negative [21].

The breast tissue samples which fail to express ER, PR, Her2 positivity by IHC are termed as triple negative breast cancer **(TNBC)** [22]. Epidemiological studies have revealed that TNBC cases exhibit a distinct feature in disease aetiology by following the significantly high rate of metastasis, tissue invasion, relapse and resistance to conventional anti-neoplastic therapies like radio or chemotherapy and hormone withdrawal therapy than hormone receptor-positive subtypes of BC [23]. Epidemiological studies from different ethnic groups in India have shown a significantly high prevalence of TNBC in both premenopausal and postmenopausal females [24-28]. A study from NER of India has shown a high number of IDC and TNBC subtypes of BC in females [29].

Classification of BC based on gene expression profiling

In recent years protein expression and gene sequencing studies have distinctly classified BC into several subtypes [30]. Molecular profiling of different subtypes of BC has revealed that TNBC subtype is significantly associated with basal-like features by expressing basal cytokeratin markers like CK-5, 14 and 17 [24,31,32]. Moreover, next-generation sequencing studies have shown that significantly high mutational rate in both BRCA1 and BRCA2 genes and a defective DNA repair mechanisms are hallmarks of TNBC subtype of BC [33-36]. Transcriptome studies have classified TNBC into two distinct basal-like subtypes, BL1 and BL2 in which BL1 subtype of TNBC is significantly associated with expressional alternations in cell cycle and DNA damage repairing pathway genes whereas BL2 subtype is marked with growth factor signalling pathways [37]. Clinical studies have shown that BL1 subtype of TNBC is significantly resistant to cisplastin whereas mesenchymal and luminal subtypes are more prone to PI3K pathway inhibitors along with the SRC inhibitor dasatinib [37]. Till date no high throughput transcriptome profiling studies has been performed to further classify BC in Indian females.

Association of reproductive status with the risk of BC in females

PBCR data has revealed that premenopausal females constitute almost 50% of total BC cases in India [38]. PBCR studies from India have shown that age-adjusted incidence of BC is significantly associated with the ethnicity [39]. Hospital-based cancer registry studies have revealed that a significant proportion of BC patients in India are under 35 years of age [39]. Hospital-based clinical studies have also shown that endocrinological alternations like shifting from male to female sex hormone ratio i.e. from androgen to oestrogen conversion, high rate of androgen biosynthesis in the ovary and low circulatory oestrogen level are significantly associated with the increased risk of BC in females [40]. However, clinical studies have revealed that BC cases with comparatively older age, especially in postmenopausal females are significantly associated with the increased positivity to respond against the adjuvant chemotherapeutic agents in comparison to the younger premenopausal females [41].

Epidemiological studies have shown that anthropogenic measures, like waist size and body mass index, female reproductive status like early onset of menarche, delayed first birth, decreased parity or null parity, short duration of lactation, use of birth control pills are significantly associated with the increased risk of BC in females [42,43]. Studies have revealed that BC incidence rate in Mumbai is highest in Parsis and Christians whereas lowest incidence rate has been reported in Jains and Buddhists [44] possibly due to late marriage, delayed first full term pregnancy and consanguineous marriage in Parsi communities [45]. Epidemiological studies conducted on females from Dravidian ethnicity in South India have shown nulliparous females have significantly high risk of BC in comparison to females having a child [43]. Epidemiological studies have demonstrated that lifetime duration of breastfeeding habit is inversely associated with the risk of BC in premenopausal females in India [42,43].

Association of dietary habits with the risk of BC in females

Molecular epidemiological studies have revealed that dietary pattern can alter cellular oxidative stress levels by interacting with the DNA repair pathway and tumour suppressor pathway associated genes in the tumour microenvironment in breast epithelial cells [46]. India being a diverse country with respect to ethnic and socio-demographic variations, food habits plays a crucial role in the risk of BC [47,48]. Epidemiological studies have shown that betel nut chewing, tobacco smoking and alcohol consumption habits are significantly associated with the increased risk of BC in females from India [49].

Epidemiological studies have shown a significant association of betel nut consumption with the increased risk of BC in females from NER of India [50]. Betel nuts are composed of various alkaloids, like arecoline, arecaidine, guvacine and guvacoline in which nitrated arecoline effectively binds with the DNA [51]. Studies have shown that such binding causes DNA adduct which are responsible for oncogenesis in the breast [13,52].

For last three decades, several epidemiological studies have been performed by different group of researchers to elucidate the association of ethanol consumption habit with the risk of BC [53,54] though the results are inconsistent and contradictory [55]. Experimental studies have shown that dietary consumed ethanol significantly alter the cell proliferation rate by modulating the expression of transcription factors associated with the ER signalling pathway [56,57]. Epidemiological studies have shown that alcohol consumption habit is significantly associated with the increased risk of BC in females from India [58].

Moreover, epidemiological studies have revealed that several dietary habits like regular consumption of fresh vegetables and fruits are significantly protective lowering the risk of BC in females in India irrespective of their ethnicity [59,60]. Studies have shown that regular consumption of leafy vegetables, beta carotene and isoflavonoid rich food are protective and significantly reduce the risk of BC in females [61].

Genetic hetero geneity with the increased risk of BC in India

Molecular epidemiological studies have shown that mutation and/or polymorphism in tumour suppressor genes, DNA repair mechanism genes, innate immune genes, metabolic genes and cytokine genes are significantly associated with the increased risk of BC in females based on their ethnic variations [62]. For last two decades several molecular epidemiological studies have been performed to investigate the genetic heterogeneity of BC in different ethnic groups of females from India [63].

Association of tumour suppressor genes with the risk of BC in females

Tumour suppressor genes are responsible for the cellular inbuilt defence mechanism by arresting cell cycle at specific checkpoints at the time of DNA replication [64]. Thus called as "guardian of the genome" [65]. Studies have revealed that mutated *TP53* is significantly associated

with the chemotherapy and radiotherapy resistance pattern in clinical outcome [66]. *In vitro* studies have shown that siRNA-mediated targeting of *TP53* gene is significantly associated with the activation of pro apoptotic genes [67]. *TP53* knockout animal models have shown a significant association of G1 checkpoint kinase 1 ***(CHK1)*** gene with the tumorigenesis in the breast [68].

Molecular epidemiological studies have revealed that proline allele at codon 72 of *TP53* gene is significantly associated with the increased risk of BC in females from North India [69] whereas no direct association of *TP53 codon* 72 polymorphism with the increased risk of BC has been found in females from NER of India [70]. However, our study has revealed that 22bp deletion in the promoter region of *TLR2* gene is significantly associated with the increased risk of BC in females from NER of India who carry proline allele at *codon* 72 of their *TP53* gene [70].

Genetic and molecular studies have shown that *BRCA1* and *BRCA2* proteins play a crucial role in the maintenance of genomic stability, DNA repair mechanism and cell cycle regulation [71,72]. Molecular epidemiological studies have shown that mutation in *BRCA1* and *BRCA2* genes are significantly associated with the increased risk of BC in females from India [12]. Moreover, it has found that mutation in *BRCA1* gene is significantly associated with the early onset of BC in females [73]. Molecular epidemiological studies from India have shown that several variants of *BRCA1* and *BRCA2* gene are significantly associated with the increased risk of BC [9,74] following a strong ethnic variation in which few variants are novel in nature [75].

Association of DNA-repair pathway genes with the risk of BC in females

Studies have shown that defect in DNA repair mechanism is significantly associated with the increased risk of BC [22]. Molecular epidemiological studies have revealed that polymorphisms in DNA-repair pathway genes can alter the nature of their protein products and thus either increase or decrease the risk of BC in females [76,77]. Among different types of DNA repair genes, *Xeroderma Pigmentosum Group D* ***(XPD)*** and *X-ray Repair Cross Complementing gene* ***(XRCC)*** have been studied globally in context to BC epidemiology in females [78].

XRCC genes are commonly known for their involvement in base excision repair **(BER)** mechanisms in small DNA lesions generally induced by oxidative stress [79]. *XRCC* genes produce multidomain protein product which is basically devoid of any catalytic activity but capable of influencing the binding of DNA polymerase *β*, DNA ligase and poly ADP-ribose polymerase **(PARP)** at the site of damaged DNA segment [80,81]. Epidemiological studies have revealed that polymorphism in *XRCC* gene is significantly associated with the increased risk of BC in females [22,82,83], though the results are inconsistent and ethnic variations persist [84].

Molecular epidemiological studies have revealed that polymorphism in *XRCC1A (Arg194Trp)* gene is significantly associated with the increased risk of BC in pre menopausal females in North India [85-87]. Studies have shown that polymorphism in *XRCC3 (Thr241Met)* gene is significantly associated with the increased risk of BC [88]. One meta-analysis has shown that *RAD51* polymorphism *(135G/C)* is significantly associated with the increased risk of BC following strong

ethnic variations [89]. Molecular epidemiological studies have also revealed that polymorphisms in *ERCC2* gene and *APEX1* genes are significantly associated with the increased risk of BC in females from North India but till date, as far our current knowledge, no molecular epidemiological studies have been performed to investigate these polymorphisms in different ethnic populations from India [87,90].

Association of immune genes with the risk of BC in females

Toll-like receptors ***(TLRs)*** form a major component of the innate defence system against invading organisms and recognise damage-associated molecular patterns **(DAMPs)** in host immune system [91,92]. Molecular epidemiological studies have revealed that the activation of *TLRs* on tumour cells initiate signalling cascades that mediate the release of cytokines and chemokines from the tumour cells in an autocrine and paracrine manner [93]. *In vitro* studies have shown that significantly high expression of TLRs on BC biopsy samples than normal healthy control groups [94, 95]. Epidemiological studies have revealed that 22bp deletion *(-196-174 del)* in *TLR2* promoter region is significantly associated with the increased risk of BC in females from NER of India [70].

Molecular epidemiological studies have shown that polymorphism in *TNF-α* gene *(-308G/A)* is significantly associated with the increased risk of BC in females from South India whereas no significant association has found in females from North India [96,97]. Another molecular epidemiological study has revealed that polymorphism in *TGF-β* gene is significantly associated with the increased risk of BC in India following strong ethnic variations [98]. Pooja *et al* have shown that *-29C/T* substitution in *TGF-β* gene is significantly increase the risk of BC in both premenopausal and postmenopausal females irrespective of their ethnicity whereas *-74G/C* substitution in *TGF-β* gene is significantly protective with the risk of BC in females from North India [98]. Moreover, studies have shown that polymorphism in *IL-1β (-3954C/T)* and *IL6 (-174G/C)* genes are significantly associated with the increased risk of BC in Indian females [99].

Other genes studied in association with increased risk of BC in females

Molecular epidemiological studies have shown that polymorphisms in *ER-α* and *ER-β* genes are significantly associated with the increased risk of BC in females from India [100,101]. Chakraborty *et al* have shown that poly-A microsatellite repeats in *vitamin D receptor* ***(VDR)*** gene is significantly associated with the increased risk of BC in Indo-European females from North India [102]. Studies have revealed that *A2454G* polymorphism in *Cytochrome P450* enzyme Superfamily ***(CYP)*** gene is significantly associated with the increased risk of BC in females from North India whereas no significant association of *T3698C* polymorphism with the increased risk of BC has found in the studied population of the same ethnicity [103,104]. Molecular epidemiological studies from NER of India have shown that the polymorphism in *GSTT1, GSTM1, GSTP1* and *CYP17* genes are significantly associated with the risk of BC where betel nut chewing habit is an important effect modifier [50].

Future Directions

In future, molecular epidemiological studies with large sample size to investigate the association of genetic heterogeneity in the genome of Indian females belonging from different ethnic groups by genome-wide association study **(GWAS)** may be helpful [105]. Moreover transcriptome study of the candidate biomarker genes by microarray or next generation sequencing **(NGS)** may be fruitful to identify novel drug targets for therapeutic purposes [63, 106].

CONCLUSION

Breast cancer is a heterogeneous disease comprising of distinct variations in risk factors, hormone receptor status and genetic heterogeneity [107]. India being ethnically and socio-economic-culturally diverse country, incidence of BC and associated risk factors are significantly variable in this vast region [107]. For future drug targeting, identification of epidemiological and genetic heterogeneity of BC in different ethnic populations in India is an utmost need for public health concerns [108]. PBCR data, hospital-based clinical studies and institutional case-control studies on different ethnic groups from India have revealed ample valuable information regarding the high prevalence of BC in India. In summary,

- Incidence of BC in India is significantly high in urban populations than rural females probably due to changes in their lifestyle habits with urbanisation,
- Studies have shown that early onset of menarche, late age of marriage, late age of first full term pregnancy, small lifetime duration of lactation, late age of menopause are significantly associated with the increased risk of BC in females from India irrespective their ethnicity.
- Population-based cancer registry **(PBCR)** data have shown that most of the BC cases in India are comparatively younger females. Thus early onset of BC in premenopausal females is an important concern.
- Epidemiological studies have shown that food habits are significantly associated with the increased risk of BC in females from India which show strong ethnic variations. It has been found that risk factors like betel nut chewing with or without tobacco, consumption of alcohol and tobacco smoking are important effect modifier in BC.
- Studies have revealed that regular consumption of fresh leafy vegetable, fresh fruit and fresh fish are significantly protective with the risk of BC in females from India.
- Molecular epidemiological studies have shown that mutation or polymorphism in tumour suppressor genes, DNA repair mechanism genes, immune pathway genes and detoxification genes are significantly associated with the increased risk of BC in Indian females following strong ethnic variations.
- Histopathological and Immunohistochemical studies have revealed that high prevalence of BC in Indian females is significantly associated with IDC type which is significantly correlating with TNBC subtype.

- Identification of candidate genes for identification of high risk group by high-throughput sequencing technologies and GWAS studies in Indian females belonging to different ethnic groups is an utmost need for early detection of BC.

ACKNOWLEDGEMENT

This study was supported by Indian Council of Medical Research **(ICMR)**.

CONFLICT OF INTEREST

None declared.

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