Title: Epidemiological study to analyze associated risk factors forbreast cancer– A retrospective case-control study

Sumati Mishra[1], Dr. Sudhir Kumar Awasthi[1], Dr. Prashant Tripathi[2], Dr. Kirti Amresh Gautam[3],Dr. Alok Raghav[3], Dr. Pramod Kumar Singh[4]

[1]Department of Life Sciences, Chhatrapati Shahu Ji Maharaj University (CSJMU), Kanpur, India

[2]Department of Biochemistry, GSVM Medical College, Kanpur, India

[3]Multidisciplinary Research Unit, GSVM Medical College, Kanpur, India

[4]JK Cancer Institute, Kanpur, India

Corresponding Author,

Sumati Mishra

Department of Life Sciences

 Research Scholar (Joint CSIR-UGC JRF qualified)

Chhatrapati Shahu Ji Maharaj University (CSJMU), Kanpur, India

Abstract:

Introduction

Breast cancer is the most common cancer among women.About 1 in 29 females will develop breast cancer during their lifetime. Breast cancer is increasing drastically due to adaptation of westernization and shifting reproductive and behavioral patterns. In this study we aimed to analyze the association between demographical details of breast cancer patients and cancer free controls and clinic-pathological presentation of Indian women with breast cancer.

Material and Methods: In this retrospectiveobservational case-control study histopathological confirmed breast cancer cases and cancer free controls were enrolled. Their demographical and personal habit data were recorded using structured questionnaire. We compared the data between cases and controls using Chi-Square test for categorical data and Student's T-test for the continuous data. Two-sided test P-values of less than 0.05 were considered as significant results.

Results: Variables including age (0.02), family history (p = 0.0001), residential area (p = 0.01), age during menopausal (p = 0.004) and habit of smoking or tobacco chewing (0.03) were also statistically significant between cases and controls. Comparison of BMI between cases and controls was marginally significant (p = 0.05). Other observed variables were not significantly correlated.

Conclusions: Establishment of comprehensive cancer including breast cancer control programs comprising awareness about the breast cancer, regulatory mechanisms, advocating for appropriate policies and programs for cancer control and early detection can be initiate.

Introduction

Globally, breast cancer is the most common type of cancer among the women resulting approximately 25% of all cancers (Ferlay et al., 2015). According to population-based cancer registries (PCBRs) breast cancer followed by cervix uteri and ovary cancer is the most common occurring cancer among Indian females and it is frequently diagnosed at the locally advanced stage (57.0%) (1). Approximately, 1,62,468 incidence and 87,090 breast cancer related deaths occurred in Indian female population (Gupta et al., 2015).With an estimate 1 in 29 females will develop breast cancer during their lifetime (0-74 years of age) (1), resultant, annual percentage of new cases ofbreast cancer ranged from 0.46 to 2.56 (2). A steep increase during 2008-2014 in incidence (11.54%) and mortality (13.82%) due to breast cancer is the major concern of multidisciplinary research (Ferlay et al., 2015; Ferlay et al., 2010). The major epidemiologicalfactors for developing breast cancer in India include adaptation of westernization culture and shifting reproductive and behavioral patterns as described in global and Indian studies (Babu et al., 2013; Balasubramaniam et al., 2013). Several risk factors have been reported with disease etiology including female gender, age, family history of breast cancer and early menarche or late menopause, post-menopausal obesity or/and therapy, exposure to radiation, higher level of endogeandage during the first gravidity (3,4; Key et al., 2001). Besides these risk factors, genetic mutation in certain genes plays significant role in the etiology of breast cancer (5). There is a significant difference in the survival rates in developed and developing countries due to inattentive about the disease, lack of early diagnosis and inadequate resources ofmedical facilities (Anonymous, 2016; Malvia et al., 2017). Globally, several epidemiological studies conducted on breast cancer correlating the associated risk factors with incidence,

prevalence although, results are inconclusive to understand disease epidemiology, pattern and burden in India (Malvia et al., 2017).

In this study, we aimed to analyze the comparative association between demographical characteristicsof breast cancer patients and cancer free controls and clinic-pathological presentationof Indian women with breast cancer to understand breast cancer epidemiology.

Materials and Methods

This retrospectiveobservational case-control studyhas the approval of Ethics Committee of GSVM Medical College, Kanpur (Ref. No. EC/BMHR/2020/46) and has been conducted at JK Cancer Institute, Multidisciplinary Research Unit and Department of Biochemistry, GSVM Medical College, Kanpur, India. Consent from the participants has been taken prior to enrollment in the study and they were notified that they can withdraw at any time if they do not want to be the part of this study. Women with histopathological confirmed diagnosis of breast cancer have been enrolled as cases during the period from January 2020 to December 2020. Women with any chronic disease along with breast cancer have excluded from the study. Women with inconclusive histopathological reports and other insufficient clinical data were also excluded from the study. Women who were visiting the hospital for other health related issues and willingness to be the part of the study were enrolled as controls during the period from January 2020 to December 2020. Close relatives of the patients such as first degree relative or mother were not recruited. All the enrolled controls were matched to cases by gender and ethnicity. Trained staff have collected the data including demographical parameters (age, sex, and ethnicity), smoking, tobacco chewing or any other personal habits and complete clinical

investigations of the disease (stage and grade)from the subjects and generated data was organized and maintained the record on Excel sheet for the further use.

The data were analyzed by using SPSS software version 21.0. We compared the data between cases and controls using Chi-Square test for categorical data and Student's T-test for the continuous data. Two-sided test P-values of less than 0.05 were considered as significant results.

Results

A total of 200 women were recruited including 90 cases of breast cancer and 110 controls free from any type of cancer during the period from January 2020 to December 2020 from the JK Cancer Institute, Kanpur, UP, India. The selected demographical details and personal habits of cases and controls have been presented in Table – 1. The mean age of cases 51.33±15.56 and controls 46.29±16.26 was statistically significant with p-value = 0.02. Comparison of BMI between cases and controls was marginally significant (p = 0.05). Variables including family history (p = 0.0001), residential area (p = 0.01) and age during menopausal (p = 0.004) were also statistically significant between cases and controls. The habit of smoking or tobacco chewing was more frequent among cases and was significantly differed (p = 0.03).

The other variables comprising age during menarche, use of oral contraceptive pills, and age during the first pregnancy and dietary habit were not statistically significant between cases and controls.

Table – 1 Demographical details of the histopathological confirmed breast cancer subjects (^{a}Chi-square test, ^{b}Unpaired t-test)

Variables	Case (90)	Control (110)	$t^*/\chi2$ Value,P value

Age	51.33±15.56	46.29±16.26	**2.22, 0.02^b**
BMI	23.68±6.23	22.09±5.18	**1.97, 0.05 ^{b}**
Family History			
Positive	17 (18.89%)	1 (0.91%)	**19.53, <0.0001^a**
Negative	73 (81.11%)	109 (99.09%)	
Residence			
Urban	39 (43.33%)	67 (60.90%)	**6.13, 0.01^a**
Rural	51 (56.67%)	43 (39.10%)	
Smoking/Tobacco			
Yes	12 (13.33%)	5 (4.54%)	**4.91, 0.03^a**
No	78 (86.67%)	105 (95.46%)	
Dietary Habit			
Vegetarian	49 (54.44%)	63 (57.27%)	0.16, 0.69^a
Non-vegetarian	41 (45.56%)	47 (42.73 %)	
Age at menarche	14.87±1.56	14.93±2.11	0.22, 0.82
Age at Menopausal	52.65±4.56	51.09±3.11	**2.86, 0.004**
Age during first pregnancy	23.65±3.58	22.39±5.48	1.87, 0.06
Oral Contraceptive			
Yes	9 (10%)	6 (5.46%)	1.47, 0.22^a
No	81 (90%)	104 (94.54%)	

Discussion

The etiology of breast cancer is extremely complex process and its onset and progression results from a seriesof epigenetic, genetic, endocrine and external environmental factors like infectious agents. These factors are majorly influenced by frequent exposure of people to carcinogens in everyday life by virtue of their habits.Experimental andepidemiological studies have identified 30-40% underlying etiological causesof breast cancer, although,remaining 60-70% are needed be explored(Momenimovahed et al., 2019).This study observed and analyzed demographical factors that might be associated or predisposed women towards the higher risk of developingbreast cancerby comparing variables between cases and controls.

The risk of being diagnosed with breast cancer increases substantially with uncontrollable factor the age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically(3). Other risk factors like smoking and occupational exposure can be controlled but person's age or family history cannot be changed. We found a strong association of breast cancer risk with the age between cases and controls that may be correlated and co-associated with the exposure of other risk factors a person faced off. In a case-control study, Mahouri and co-investigators has also been observed higher incidence rate in women age more than 50 years (Mahourai et al., 2007).Although, breast cancer in younger women mostly diagnosed in advanced stages with lymph nodes involved and poor survival is the major concern of cancer awareness (Assi et al., 2013).Alcohol and tobacco consumption is an established risk factor, women who consumed three or more alcoholic drinks per day are associated with 30-50% increased risk developing breast cancer (6)(Momenimovahed et al., 2019).Supporting the previous evidence this study also found an increased risk of developing breast cancer among women consumed alcohol and tobacco.According to a published article, cigarettes smoked per

day and number of years of smoking before the first childbirth is also associated with risk of developing cancer (Bjerkaas et al., 2013).

Currently, well-established evidence of breast-cancer risk has shown that early age at first term birth is related to life time reduction in risk; increased parity is associated with a long-term risk reduction, a nulliparous woman has roughly the same risk as a woman with a first term birth aged about 30 years (7). Several published article have reported younger age during menarche positively associated with breast cancer risk (Kim et al., 2015; Thakur P et al., 2017; Laamiri et al., 2015), although we did not find such association with studied population.

With reference to exogenous hormones, the risk of breast cancer is 15-25% higher in current and recent users of oral contraceptives (OC) as compared to never users (8). The evidence derived both from observational epidemiological studies (cohort and case-control) and randomized clinical trials indicates that the risk of breast cancer incidence and mortality (mainly ductal cancer) is elevated among women using combined hormonal replacement therapy (HRT) (Beral et al., 1997;Beral et al., 2003). Estradiol concentrations in the blood have been directly associated with breast cancer risk in post-menopausal women, particularly with estrogen and progesterone receptor positive tumors (9).Contradictory to previous report the current study did not found any significant relationship with hormonal therapy and increased risk of breast cancer, this insignificant association may be due to the limited use of oral contraceptive pills or other hormonal therapy among the female population(Beaber et al., 2014; Kotsopoulos et al., 2014).

Based on various studies family history of breast cancer is the major risk factor even in those women who are not a carrier of BRCA mutation (Thakur P et al., 2017; Flavarjani et al., 2014;

Bravi et al., 2018; Ahern et al., 2017; Sweeney et al., 2004).We also found a strong relationship between family history and risk of breast cancer (p = 0.0001).

A health study showed that intake of animal fat mainly from red meat and high-fat dairy foods before menopause was associated with a heightened risk of breast cancer (10) (Thakur P et al., 2017). Data from five prospective studies were combined to compare the death rates of vegetarians from common diseases with those of non-vegetarians with similar lifestyles. Compared with regular meat eaters, mortality from ischemic heart disease was 20% lower in occasional meat eaters, 34% lower in people who ate fish but not meat, 34% lower in lacto-ovo-vegetarians, and 26% lower in vegans. No significant differences were recorded between vegetarians and non-vegetarians in the mortality rates of breast cancer (11). The results of the present study support the previously published reported data.

Cancer is a preventive disease and can be controlled by public awareness and policies that focus on restriction or under observation use of products or material that are carcinogenic or by changing the life-style or personal habit, etc. Some such behavioral factors — delayed childbearing, lower parity, and reduced breast-feeding are becoming more prevalent in lower income countries (4). These can be reduced by adapting behavioral changes. Early detection of cancer can also reduce the economic burden spend on the cancer therapy.As evidence several studies have been observed whether intake of fruit, vegetables and micronutrients, dietary fibers, dairy products, total and saturated fats, glycemic index and load and intake of phytoestrogens have an influence on breast cancer risk(Momenimovahed et al., 2019). No association emerged consistently from prospective studies, although there is some evidence for a protective role played by soy intake and folate (12). Results frompooled analysis of eight prospective studies

suggest that fruit and vegetable consumption during adulthood is not significantly associated with reduced breast-cancer risk (13).

Limitations – this study was conducted and comprised women majorly belong to Northern part of India. Therefore, the obtained data cannot be generalized to Indian population. The study was a retrospective study and collected data were based on the recollection of the patient's about past life events also includes some personal information that may deviate from the actual information due to their feeling and behavior. Since the researcher was limited for the duration of one year and therefore, the number of enrolled subjects constrained for the one year. Lastly, the grading andstaging of the cancerwas not compared among the breast cancer women and recorded data.

In conclusion, the findings of this retrospective observational case-control study found key indicators that can modulate the risk of developing breast cancer and set a mark for policy makers for increasing efforts for designing and establishing comprehensive screening programbased on scientific and experimental bases comprising awareness about the breast cancer, advocating for appropriate policies and programs for cancer control and early detection.

Acknowledgment:

References:

1. Mathur P, Sathishkumar K, Chaturvedi M, et al. Cancer Statistics, 2020: Report from National Cancer Registry Programme, India. JCO Global Oncol 2020;6:1063-1075.

2. Rangarajan B, Shet T, Wadasadawala T, et al. Breast cancer: An overview of published Indian data. South Asian J Cancer 2016;5(3):86-92.

3. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, riskfactors, and genetics. BMJ. 2000;321:624-628.

4. Porter P. ''Westernizing'' women's risks? Breast cancer in lower-income countries. N Engl J Med. 2008;358:213-216.

5. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. New England Journal of Medicine 1985;312(3):146-51

6. Hamajima N, Hirose K, Tajima K, Rohan T, et al. Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58, 515 women with breast cancer and 95,067 women without the disease. Br J Cancer. 2002;87:1234-1245.

7. Henderson BE, Pike MC, Bernstein L, Ross RK. Breast cancer. In: Schottenfeld D, Fraumeni JF, eds. Cancer epidemiology and prevention. 2nd edn. Oxford University Press: New York, 1996.

8. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. The Lancet 1996;347(9017):1713-1727.

9. Key T, Appleby P, Barnes I, Reeves G; Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst. 2002;94:606-616.

10. Cho E, Spiegelman D, Hunter DJ, et al. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst. 2003;95:1079–1085.

11. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA. 1998;279:535-540.

12. Larsson SC, Giovannucci E, Wolk A. Folate and risk of breast cancer: a meta-analysis. J Natl Cancer Inst. 2007;99:64-76.

13. Smith-Warner SA, Spiegelman D, Yaun SS, et al. Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA. 2001;285:769-776.

14. Ahern TP, Sprague BL, Bissell MC, et al. Family history of breastcancer, breast density, and breast cancer risk in a US breast cancerscreening population. Cancer Epidemiol Biomarkers Prev. 2017;26(6):938–944.

15. Anonymous. Three Year Report of Population Based Cancer Registries 2012–2014. Indian Council of Medical Research (ICMR), Bangalore, India 2016.

16. Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS.Epidemiology and prognosis of breast cancer in youngwomen. J Thorac Dis. 2013;5(Suppl 1):S2–S8.

17. Beaber EF, Buist DSM, Barlow WE, et al.Recentoral contraceptive use by formulation and breast cancer risk amongwomen 20 to 49 years of age. Cancer Res. 2014;74(15):4078–4089.

18. Beral V, Bull D, Doll R, Key T, Peto R, Reeves G. Breast cancer andhormone replacement therapy: collaborative reanalysis of data from 51epidemiological studies of 52, 705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350(9084):1047–1059.

19. Beral V; Million Women Study Collaborators.Breast cancer andhormone-replacement therapy in the Million Women Study.Lancet.2003;362(9382):419–427.

20. Bjerkaas E, Parajuli R, Weiderpass E, et al. Smoking durationbefore first childbirth: an emerging risk factor for breast cancer?Results from 302,865 Norwegian women.Cancer Causes Control.2013;24(7):1347–1356.

21. Bravi F, Decarli A, Russo AG. Risk factors for breast cancer in a cohortof mammographic screening program: a nested case-control studywithin the FRiCaM study. Cancer Med.2018;7(5):2145–2152.

22. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidenceand mortality worldwide: sources, methods and major patternsin GLOBOCAN 2012. Int J Cancer 2015; 136: E359–86.

23. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, ParkinDM. Estimates of worldwide burden of cancer in 2008:GLOBOCAN 2008. Int J Cancer 2010; 127: 2893–917.

24. Flavarjani AM, Hedayatpour B, Nourian SM, Bashardoost N. Studyof the association between blood types and breast cancer among Isfahanianwomen with breast cancer. Adv Biomed Res. 2014;3(1):43.

25. Gupta A, Shridhar K, Dhillon PK. A review of breast cancerawareness among women in India: cancer literate or awarenessdeficit? Eur J Cancer 2015; 51: 2058–66.

26. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. The Lancet Oncology 2001;3(3):133-140.

27. Kim Y, Yoo K-Y, Goodman MT. Differences in Incidence, Mortality andSurvival of Breast Cancer by Regions and Countries in Asia and ContributingFactors. Asian Pac J Cancer Prev. 2015;16(7):2857–2870.

28. Kotsopoulos J, Lubinski J, Moller P, et al; Hereditary Breast CancerClinical Study Group.Timing of oral contraceptive use and the risk ofbreast cancer in BRCA1 mutation carriers. Breast Cancer Res Treat.2014;143(3):579–586.

29. Laamiri FZ, Bouayad A, Hasswane N, Ahid S, Mrabet M, Amina B.Risk Factors for Breast Cancer of Different Age Groups: MoroccanData? Open J Obstet Gynecol. 2015;05(02):79–87.

30. Malviya S, Bagadi SA, Dubey US, Saxena S. Epidemiology of Breast cancer in Indian women. Asia-Pacific Journal of Clinical Oncology 2017;13:289-295.

31. Momenimovahed Z and Salehiniya H. Epidemiology characteristics of and risk factors for breast cancer in the world. Breast Cancer – Targets and Therapy 2019;11:151-164.

32. Sweeney C, Blair CK, Anderson KE, Lazovich D, Folsom AR.Risk factors for breast cancer in elderly women. Am J Epidemiol.2004;160(9):868–875.

33. Thakur P, Seam RK, Gupta MK, Gupta M, Sharma M, Fotedar V.Breast cancer risk factor evaluation in a Western Himalayan state: Acase–control study and comparison with the Western World. SouthAsian J Cancer. 2017;6(3):106–109.