Underweight Indian Women at a Risk for Developing Breast Cancer: A Retrospective Study

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Background: Breast cancer is the leading cancer diagnosed in Indian women. Lifestyle related factors such as high body mass index (BMI) and obesity have been recognized as major risk factors for the development of breast cancer. However, India has higher proportion of underweight population and recently positive correlation has been reported between underweight and increased risk of breast cancer. We have attempted to study an association between low BMI and total body fat percentage with breast cancer risk by performing retrospective analysis on a small sample size of 41 female patients diagnosed with breast cancer. The data was collected from Department of Oncology, Bharati Vidyapeeth Hospital and Research Centre (BVHRC), Pune, India.

Methods: Binary logistic regression was performed to estimate odds ratios (ORs) and to examine the predictive effect of each factor on the breast cancer risk.

Results: It was observed that underweight population displayed higher risk of breast cancer development based on BMI (OR-15.40) and body fat % (OR-1.33).

Conclusion: This pilot study suggests that low body mass index may be related to poor prognosis in breast cancer and thus warrants further studies on a larger sample size to establish a positive correlation.

Introduction

India has the highest number of underweight adults in the world [1]. Epidemiological studies conducted in different geographical areas of India have suggested an association between low body mass index and increased risk of mortality and health-related quality of life [2]. In India, breast cancer is the leading cancer diagnosed in women. According to Indian Council of Medical Research (ICMR) report, based on cancer registries from different parts of India, number of breast cancer cases were predicted to rise by 85% in 2020 [3]. Lifestyle related risk factors such as high body mass index (BMI) and obesity have been recognized as independent risk factors for the development of breast cancer by many researchers [4, 5]. Various studies have demonstrated a positive correlation between obesity and incidence of breast cancer that would affect the survival of postmenopausal women with breast cancer [6-8].

However, several studies have suggested that breast cancer patients who are underweight could be at a higher risk than normal weight for recurrence and mortality [4, 9-11]. Recently, low BMI in young breast cancer patients with lymph node metastases, was reported to be of prognostic significance [12]. It has been hypothesized that a low BMI may result in lack of breast fat resulting into lower levels of ovarian hormones in the early adult life, which may lead to increased risk of breast cancer [13]. Thus, the present study has attempted to establish a correlation between lower BMI and total body fat with breast cancer risk.

Materials and Methods

Study population

The present retrospective study included 41 females diagnosed with breast cancer (cases) and 24 healthy females (control), who visited Department of Surgery and Oncology, Bharati Vidyapeeth Hospital and Research Centre (BVHRC), Pune, India during the period of 2014- 2016 (Ethics approval no.- BVDU/MC/02).

Data collection

Information on anthropometric factors of cases such as age, weight, height and body fat percentage was collected from the hospital records of Department of Surgery and Oncology, BVHRC. BMI was calculated as weight in kilograms divided by height in meters square (kg/m^2). Controls were selected among females who visited awareness camp organized by BVHRC. Females aged below 30 and above 80, diagnosed with gynecological malignancies were excluded from the control study population.

Statistical analysis

Descriptive statistics was used to describe the data. For quantitative variables, mean with standard deviation and for qualitative variables, frequency with percentage was used to describe the data. Chi-Square test and independent sample t test were performed to assess the significance of age, weight, height, BMI and total body fat percentage between breast cancer patients and controls. Binary logistic regression was performed to estimate odds ratios (ORs) and to examine the predictive effect of each factor on the risk for breast cancer. All the statistical assessments were two-sided and considered to be significant with p-value <0.05. All the statistical analysis were performed by using STATA15 software.

Results

Characteristics of the study population

In this study, mean age of breast cancer cases and controls was 54.12 ± 13.42 and 49.54 ± 11.98 years, respectively (Table 1).

Variables	Breast cancer cases (n= 41)	Controls (n=24)	P value
Age (years)	54.12 ± 13.42	49.54 ± 11.98	0.1724
Height (cms)	156.8 ± 4.74	150.3 ± 6.25	< 0.001*
Weight (Kgs)	51.76 ± 10.42	52.47 ± 10.28	0.7894
Body mass index (BMI)	21.03 ± 4.00	23.17 ± 4.01	0.0420 *
Body fat %	25.85 ± 5.24	27.93 ± 8.67	0.2307

Table 1. Characteristics of Study Population.

Data has been represented as Mean ± SD; * p < 0.05, * * p < 0.01, *** p < 0.001

Mean height of cases and controls was 156.8 ± 4.74 cm and 150.3 ± 6.25 cm, respectively. The study cases weighed between 42-79 kg while the controls weighed between 33.5-77 kg, thereby

showing that the mean weights were similar for both the groups (51.76 kg and 52.47 kg, respectively) (p= 0.2307). Mean BMI of breast cancer cases and controls was 21.03 ± 4.00 and 23.17 ± 4.01, respectively whereas mean body fat % was 25.85 ± 5.24 and 27.93 ± 8.67, respectively.

BMI as a risk factor for breast cancer

Among the breast cancer cases, 53.65% showed low BMI (<18.5), 24.39% showed normal BMI (18.5-24.9%) and 21.95% showed high BMI (25-29.9/≥30) and the cases were categorized into underweight, normal and overweight/ obese groups, respectively (Table 2).

Variable (BMI)	No. of Breast cancer cases (%)	No. of Controls (%)	OR (95%confidence interval)	P value
Underweight (<18.5)	22 (53.65)	02 (8.33)	15.40 (2.92 to 80.98)	0.0010 ***
Normal (18.5 - 24.9)	10 (24.39)	14 (58.33)	1	
Overweight/ Obese (25 - ≥30)	09 (21.95)	08 (33.33)	1.57 (0.45 to 5.50)	0.477
Total	41	24		

Table 2. Association between BMI and Risk of Breast Cancer.

Abbreviations, OR- odds ratio, BMI- body mass index; * p < 0.05, * * p < 0.01, *** p < 0.001

Odds ratio above 1 demonstrated the predictive effect of high risk for each factor. Based on BMI, underweight population displayed nearly 15-fold higher risk (OR = 15.40 and p <0.0005) of developing breast cancer compared to overweight cases (OR= 1.57 and p <0.477). Thus, BMI classification showed a significant association with breast cancer occurrence.

Body fat percentage as a risk factor for breast cancer

The number of underweight breast cancer cases showing low body fat percentage were 60.97%, which was higher than the number of healthy underweight controls (33.33%) with an OR of 1.33 (p<0.0636) (Table 3).

Variable (Body fat %)	No. of Breast cancer cases (%)	No. of Controls (%)	OR (95%confidence interval)	P value
Underweight (10-25%)	25 (60.98)	08 (33.33)	1.33 (0.27 to 6.43)	0.0636
Normal (26-31%)	07 (17.07)	03 (12.50)	1	
Overweight/ Obese (31.1- 40% or more)	9 (21.95)	13 (54.17)	0.30 (0.06 to 1.46)	0.136
Total	41	24		

Table 3. Association between Body Fat Percentage and Risk of Breast Cancer.

Abbreviations, OR- odds ratio, * p < 0.05, * * p < 0.01, *** p < 0.001

However, number of overweight breast cancer cases constituted 21.95% compared to 54.17% of healthy overweight controls with an odds ratio of 0.30 (p <0.136). Thus, based on body fat percentage too, underweight population displayed a higher risk of developing breast cancer.

Discussion

In this study, we have attempted to find an association between BMI and body fat levels as risk factor for breast cancer. The study was conducted on a pilot scale and the cases have not been stratified with respect to hormone receptor or menopausal status. We found that underweight (BMI <18.5) breast cancer cases displayed nearly 15-fold higher risk for the disease. Based on body fat percentage, the proportion of underweight females was higher among breast cancer patients than among healthy controls.

The complex relationship between obesity and breast cancer has been studied at various levels such as BMI, different measures of obesity, hormonal or menopausal status in patients, ethnicity, stage of cancer and so on. Overweight women have been reported to have increased risk for developing breast cancer (OR =2.29) compared to women with normal BMI in both pre- and post-menopausal cases [14]. Many studies have shown that there was a higher risk of breast cancer incidence among postmenopausal women with high BMI [6-8, 15]. Based on ethnicity, a positive association between high BMI and increased breast cancer incidence has been observed in the Asia Pacific group than in the European-Australian or North-American group [16]. In India, few studies have shown a positive correlation between body mass index and breast cancer risk [17-20]. Using only BMI as an indicator for weight status overshadows other parameters such as body composition, adiposity, and adipose distribution [21]. Asian population have higher levels of total body fat, more abdominal fat and less-lean mass than other ethnic groups [22]. High central obesity (measured by waist to hip ratio) was reported to be the most important risk factor of BCa, irrespective of menopausal and hormonal receptor status [4, 23]. Postmenopausal women with a normal BMI but high body-fat levels [24] or high central obesity [8] were shown to have an elevated risk of breast cancer.

In the current work, we have categorized the sample population into underweight, normal and overweight/ obese, based upon BMI and body fat percentage. We observed that low BMI and low total fat in underweight cases, positively correlated with breast cancer risk. Although most of the studies have underlined a positive association between high BMI and increased risk of breast cancer, few reports have indicated that underweight pose a high risk for developing breast cancer. Underweight patients were reported to be at an increased risk of local recurrence among all types of breast cancer [9]. Women with low BMI have increased risk for premenopausal breast cancer compared to those with healthy BMI [25-28]. A hospital based case control study conducted in Mumbai, India has reported a positive association between low BMI and increased breast cancer risk with high odds-ratio [4]. A multicentric study has shown association between low BMI and high risk of premenopausal breast cancer with increase in hazard ratios [29]. Underweight premenopausal women (BMI <18.5) with Luminal A and HER2 subtypes have shown risk for breast cancer [11]. A retrospective study in Chinese patients has suggested adverse outcomes in young underweight BMI (<18.5) patients (under 40 years old) with lymph node metastasis [12]. Various mechanisms have been proposed underlying the association between underweight and breast cancer risk, out of which malnutrition is one of the important factors [30]. Malnutrition often leads to immune system dysfunction that may hamper tumor surveillance by immune cells and may also influence the efficacy of systemic antitumor therapies, thereby resulting into tumor dysregulation [31].

Our findings have important joint implications wherein a positive association was observed between low BMI, low total body fat and increased breast cancer risk. This underlines the significance of body fat in underweight population, which until now was not considered as a major risk factor. The present study has several limitations, the main one being the sample size. This pilot study warrants

further studies on a larger sample size. Secondly, the patients need to be stratified based upon pre- and post-menopausal status, stage of cancer and hormone receptor status. This would strengthen our findings and further reiterate the significance of low BMI and low total body fat as important prognostic factors for management of breast cancer.

In conclusion, our study suggests that underweight status, based upon both low BMI and low total body fat, should be considered as a high-risk factor for breast cancer development and thus strategies should be developed accordingly for the prevention and management.

Acknowledgements

References

References

1. Dutta Mili, Selvamani Y, Singh Pushpendra, Prashad Lokender. The double burden of malnutrition among adults in India: evidence from the National Family Health Survey-4 (2015-16). *Epidemiology and Health.* 2019; 41DOI
2. Selvamani Y., Singh Pushpendra. Socioeconomic patterns of underweight and its association with self-rated health, cognition and quality of life among older adults in India. *PLOS ONE.* 2018; 13(3)DOI
3. Bray F, Colombet M, Mery L, et al. (2017).(eds): Cancer Incidence in Five Continents, Volume XI. Lyon, France, IARC Sci. Publ. :.
4. Nagrani Rajini, Mhatre Sharayu, Boffetta Paolo, Rajaraman Preetha, Badwe Rajendra, Gupta Sudeep, Romieu Isabelle, Parmar Vani, Dikshit Rajesh. Understanding rural–urban differences in risk factors for breast cancer in an Indian population. *Cancer Causes & Control.* 2015; 27(2)DOI
5. Rai Rajesh Kumar, Fawzi Wafaie Wahib, Bromage Sabri, Barik Anamitra, Chowdhury Abhijit. Underweight among rural Indian adults: burden, and predictors of incidence and recovery. *Public Health Nutrition.* 2017; 21(4)DOI
6. Neuhouser Marian L., Aragaki Aaron K., Prentice Ross L., Manson JoAnn E., Chlebowski Rowan, Carty Cara L., Ochs-Balcom Heather M., Thomson Cynthia A., Caan Bette J., Tinker Lesley F., Urrutia Rachel Peragallo, Knudtson Jennifer, Anderson Garnet L.. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk. *JAMA Oncology.* 2015; 1(5)DOI
7. Gravena Angela Andréia França, Romeiro Lopes Tiara, Demitto Marcela de Oliveira, Borghesan Deise Helena Pelloso, Dell' Agnolo Cátia Millene, Brischiliari Sheila Cristina Rocha, Carvalho Maria Dalva de Barros, Pelloso Sandra Marisa. The Obesity and the Risk of Breast Cancer among Pre and Postmenopausal Women. *Asian Pacific Journal of Cancer Prevention.* 2018; 19(9)DOI
8. Park Yong-Moon Mark, White Alexandra J., Nichols Hazel B., O'Brien Katie M., Weinberg Clarice R., Sandler Dale P.. The association between metabolic health, obesity phenotype and the risk of breast cancer. *International Journal of Cancer.* 2017; 140(12)DOI
9. Moon Hyeong-Gon, Han Wonshik, Noh Dong-Young. Underweight and Breast Cancer Recurrence and Death: A Report From the Korean Breast Cancer Society. *Journal of Clinical Oncology.* 2009; 27(35)DOI
10. Tan F XH, Gummadi S, et al. Impact of Body Mass Index on Prognosis for Breast Cancer Patients. *jwhg.* 2019; 6(3)DOI

11. Jeong Seok Hun, An Yoonsuk, Ahn Choonghyun, Park Boyoung, Lee Min Hyuk, Noh Dong-Young, Park Sue K.. Body mass index and risk of breast cancer molecular subtypes in Korean women: a case–control study. *Breast Cancer Research and Treatment.* 2019; 179(2)DOI

12. Chen Bo, Lai Jianguo, Guo Liping, Dai Danian, Chen Rong, Wei Guangnan, Liao Ning. Adverse effects of being underweight on young female breast cancer patients with lymph node metastases. *Journal of Cancer.* 2020; 11(7)DOI

13. Suzuki Reiko, Saji Shigehira, Toi Masakazu. Impact of body mass index on breast cancer in accordance with the life-stage of women. *Frontiers in Oncology.* 2012; 2DOI

14. Elkum Naser, Al-Tweigeri Taher, Ajarim Dahish, Al-Zahrani Ali, Amer Suad M Bin, Aboussekhra Abdelilah. Obesity is a significant risk factor for breast cancer in Arab women. *BMC Cancer.* 2014; 14(1)DOI

15. Benn Marianne, Tybjærg-Hansen Anne, Smith George Davey, Nordestgaard Børge Grønne. High body mass index and cancer risk—a Mendelian randomisation study. *European Journal of Epidemiology.* 2016; 31(9)DOI

16. Wang Jun, Yang Dong-Lin, Chen Zhong-Zhu, Gou Ben-Fu. Associations of body mass index with cancer incidence among populations, genders, and menopausal status: A systematic review and meta-analysis. *Cancer Epidemiology.* 2016; 42DOI

17. Kapil Umesh, Deo SVS, Singh P, Shukla NK, Dwivedi SN. Association of overweight and obesity with breast cancer in India. *Indian Journal of Community Medicine.* 2011; 36(4)DOI

18. Inamdar Padmanabh, Mehta Garima. Correlation Between Obesity and High Density Lipoprotein Cholesterol (HDL-C) in Breast Cancer Patients of Southern Rajasthan. *Indian Journal of Surgical Oncology.* 2011; 2(2)DOI

19. Naushad Shaik Mohammad, Hussain Tajamul, Al-Attas Omar S., Prayaga Aruna, Digumarti Raghunadha Rao, Gottumukkala Suryanarayana Raju, Kutala Vijay Kumar. Molecular insights into the association of obesity with breast cancer risk: relevance to xenobiotic metabolism and CpG island methylation of tumor suppressor genes. *Molecular and Cellular Biochemistry.* 2014; 392(1-2)DOI

20. Antony MP, Surakutty B, Vasu TA, Chisthi, M (2018). Risk factors for breast cancer among Indian women: A case–control study. Niger. J. Clin. Pract., 21-4..

21. Bandera Elisa V, Chandran Urmila, Zirpoli Gary, Gong Zhihong, McCann Susan E, Hong Chi-Chen, Ciupak Gregory, Pawlish Karen, Ambrosone Christine B. Body fatness and breast cancer risk in women of African ancestry. *BMC Cancer.* 2013; 13(1)DOI

22. Misra Anoop. Ethnic-Specific Criteria for Classification of Body Mass Index: A Perspective for Asian Indians and American Diabetes Association Position Statement. *Diabetes Technology & Therapeutics.* 2015; 17(9)DOI

23. Barberio Amanda M., Alareeki Asalah, Viner Benjamin, Pader Joy, Vena Jennifer E., Arora Paul, Friedenreich Christine M., Brenner Darren R.. Central body fatness is a stronger predictor of cancer risk than overall body size. *Nature Communications.* 2019; 10(1)DOI

24. Iyengar Neil M., Arthur Rhonda, Manson JoAnn E., Chlebowski Rowan T., Kroenke Candyce H., Peterson Lindsay, Cheng Ting-Yuan D., Feliciano Elizabeth C., Lane Dorothy, Luo Juhua, Nassir Rami, Pan Kathy, Wassertheil-Smoller Sylvia, Kamensky Victor, Rohan Thomas E., Dannenberg Andrew J.. Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index. *JAMA Oncology.* 2019; 5(2)DOI

25. Wada K., Nagata C., Tamakoshi A., Matsuo K., Oze I., Wakai K., Tsuji I., Sugawara Y., Mizoue T., Tanaka K., Iwasaki M., Inoue M., Tsugane S., Sasazuki S.. Body mass index and breast cancer risk in Japan: a pooled analysis of eight population-based cohort studies. *Annals of Oncology.* 2014; 25(2)DOI

26. Mamun Abdullah A., Finlay Jocelyn E.. Shifting of undernutrition to overnutrition and its determinants among women of reproductive ages in the 36 low to medium income countries. *Obesity Research & Clinical Practice.* 2015; 9(1)DOI

27. Engmann Natalie J., Golmakani Marzieh K., Miglioretti Diana L., Sprague Brian L., Kerlikowske Karla. Population-Attributable Risk Proportion of Clinical Risk Factors for Breast Cancer. *JAMA Oncology.* 2017; 3(9)DOI

28. Kim Joo Heung, Yoon Kwang Hyun, Hur Ho, Park Seho, Kim Jee Ye, Park Hyung Seok, Kim

Seung Il, Cho Young Up, Park Byeong-Woo. Prevalence of breast cancer-related risk factors in underweight premenopausal women: the Korea National Health and Nutrition Examination Survey IV–VI. *Breast Cancer Research and Treatment.* 2018; 174(2)DOI

29. Schoemaker Minouk J., Nichols Hazel B., Wright Lauren B., Brook Mark N., Jones Michael E., O'Brien Katie M., Adami Hans-Olov, Baglietto Laura, Bernstein Leslie, Bertrand Kimberly A., Boutron-Ruault Marie-Christine, Braaten Tonje, Chen Yu, Connor Avonne E., Dorronsoro Miren, Dossus Laure, Eliassen A. Heather, Giles Graham G., Hankinson Susan E., Kaaks Rudolf, Key Timothy J., Kirsh Victoria A., Kitahara Cari M., Koh Woon-Puay, Larsson Susanna C., Linet Martha S., Ma Huiyan, Masala Giovanna, Merritt Melissa A., Milne Roger L., Overvad Kim, Ozasa Kotaro, Palmer Julie R., Peeters Petra H., Riboli Elio, Rohan Thomas E., Sadakane Atsuko, Sund Malin, Tamimi Rulla M., Trichopoulou Antonia, Ursin Giske, Vatten Lars, Visvanathan Kala, Weiderpass Elisabete, Willett Walter C., Wolk Alicja, Yuan Jian-Min, Zeleniuch-Jacquotte Anne, Sandler Dale P., Swerdlow Anthony J.. Association of Body Mass Index and Age With Subsequent Breast Cancer Risk in Premenopausal Women. *JAMA Oncology.* 2018; 4(11)DOI

30. Sengupta Angan, Angeli Federica, Syamala Thelakkat S., Dagnelie Pieter C., Schayck C.P. van. Overweight and obesity prevalence among Indian women by place of residence and socio-economic status: Contrasting patterns from 'underweight states' and 'overweight states' of India. *Social Science & Medicine.* 2015; 138DOI

31. Bourke Claire D., Berkley James A., Prendergast Andrew J.. Immune Dysfunction as a Cause and Consequence of Malnutrition. *Trends in Immunology.* 2016; 37(6)DOI