Relationship Between Formulaic Breast Volume And Risk Of Breast Cancer Based On Linear Measurement

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Abstract

Background: Whether breast volume is a risk factor for breast cancer has been controversial. This study aimed to evaluate whether or not the significant association between breast volume and risk of breast cancer based on linear measurement by applying Propensity Score Matching (PSM) was present.

Methods: The study was designed as a hospital-based case-control study. Between March 2018 and May 2019, 208 cases and 340 controls were retrospectively reviewed. Information on menarche, smoking, feeding mode, oral contraceptives, reproductive history and family history was obtained through a structured questionnaire. Calculate breast volume using formula based on the linear measurement of breast parameters. Cox regression and PSM were used to estimate odds ratios and 95% confidence intervals for breast cancer by risk factors adjusted for potential confounders.

Results: There was a significant difference in breast volume between two groups before Propensity Score Matching(P=0.014) : P=0.009, OR=1.002, 95% CI: 1.000~1.003). Binary logistic regression showed that the risk of breast cancer was slightly higher in the case group with larger breast volume than in the control group（P=0.009, OR=1.002， 95%CI：1.000～1.003). However, there was no significant statistical difference between two groups in independent sample Mann-Whitney U test (P=0.438) and in conditional logistic regression (P=0.446).

Conclusions: After PSM for the potential confounders factors, the breast volume of cases did not differ from that of controls. The risk of breast cancer may not related to breast volume in Chinese women.

Background

In recent years, breast cancer has jumped to the top of the incidence of cancer among women. In United States of America, the number of new cases of breast cancer in women from 2011 to 2015 is 126.0 per 100,000 women per year. only in United States of America, there were expected to be 266,120 new cases of female breast cancer, with an estimated 40,920 deaths from breast cancer in 2018[1]. Up to 12.4% of women will be diagnosed with breast cancer. In China, the incidence of breast cancer has consistently ranked first among women in cancer incidence. Studies have shown that age at menarche[2], age at first pregnancy[3], feeding mode[4], family history of breast cancer[5], age[6], BMI[7], alcohol consumption[8], smoking[9], history of proliferative benign breast disease[10], oral contraceptives[11], abortion[12], breast density[13, 14], history of hyperthyroidism[15], etc., even night shift work[16], exercise[17], diet[18] was related to the onset of breast cancer, regrettably no consensus has been reached[19, 20]. In short, the breast volume has not been included in the traditional breast cancer risk list.

With the popularity of breast augmentation, more and more people were paying attention to the safety of breast augmentation surgery. Berkel et al.[21] found that women who undergo breast augmentation with silicone implants have a lower risk of breast cancer than the general population when studied the relationship between breast augmentation and breast cancer risk. This finding suggested that these women were drawn from a population already at low risk. Hsieh et al.[22] found that premenopausal women who do not wear bras had half the risk of breast cancer compared with bra users (*P* about 0.09), possibly because they likely to have smaller breasts. Boice et al.[23] found there was a protective effect following partial removal of breast glandular tissue. A study of over 30,000 women with long-term follow-up also offered a evidence that women undergoing breast reduction surgery have reduced breast cancer risk[24]. This also suggested a relationship between breast volume and the risk of breast cancer. However, in a population-based nested case-control study, Thurfjell et al.[25] found that small breast size was associated with increasing breast risk. This may be related to breast density. Eriksson et al.[26] described the relationship between breast size and breast cancer risk from a genetic perspective, failing to define the relationship between the two. Therefore, more research is needed to clarify the relationship between breast volume and the risk of breast cancer.

To help in better providing a theoretical basis for breast cancer prevention, we conducted the present study designing to defining the association between breast volume and risk of breast cancer. Longo's[27] breast volume measurement formula was used to calculate the breast volume by linear measurement data.

Methods

Patients and procedures

This retrospective hospital-based case-control study was conducted to investigate the association between breast volume and risk of breast cancer among women, involving 208 cases and 340 controls from March 2018 to May 2019 in two hospitals in Guangdong Province, one of which was a tertiary hospital with nearly 3,000 beds. Since the measurer of the study communicates with the person being measured one-on-one, the sample missing caused by the lost interview is not considered. The case group included women diagnosed with breast cancer, while the control group involved women who underwent a health check and excluded breast cancer within one month. The case group and the control group were recruited in a ratio of 1:1. Considering the success rate of PSM, we additionally increase the number of cases in the control group.Adult women who had newly been diagnosed with breast cancer by pathology or cytology were enrolled in the case group, excluding those who was characteristic by pregnant or breast-feeding, breast cancer surgery, breast mass, breast augmentation, and communication difficulties. Healthy adult women who were examined at the hospital to exclude breast cancer were enrolled in the control group, excluding those who was characteristic by pregnant or breast-feeding, breast augmentation, suspected breast cancer, and communication difficulties.

Information on sociodemographic characteristics, age at menarche, alcohol consumption, smoking, history of proliferative benign breast disease, feeding mode, oral contraceptives, and reproductive history, family history of breast cancer was obtained through a structured questionnaire. The breast parameters of the two groups were measured respectively, and calculate breast volume using formula based on the linear measurement of breast parameters.

Exposure and covariate determination

The only exposure factor for this study was breast volume, which was calculated from the linear measurement using the BREAST-V formula. Breast volume as a continuous variable, other variables such as age, height, weight, age at menarche, age at first pregnancy, number of pregnancies, feeding mode, history of proliferative benign breast disease, history of oral contraceptives, smoking, alcohol consumption, history of hyperthyroidism, family history of breast cancer was assessed at the baseline level of the questionnaire.

Breast linear measurement data collection

All data in this study were collected by in-person interview after consent was obtained from all study participants, and the bilateral breast data were collected. Grouping is a single blind to the measurer. Anatomical distances included in the BREAST-V formula were sternal notch-to-nipple distance; fold-to-nipple distance; fold-to-fold projection distance when the measured person took the standing position.

Statistical Analysis

This study was a case-control study, and all data were entered by two people after verification. Using the SPSS 24.0, the Propensity Score Matching module (PSM) was applied, and the match tolerance value was 0.005. Propensity score analysis was used to control factors that may confound the relationship between breast volume and risk of breast cancer. The propensity value calculated according to the logistic regression was matched according to the 1:1 nearest neighbor matching method, and then the two matched groups were regarded as independent group. The baseline data were statistically analyzed before and after the matching. The normal distribution measurement data was described as $M \pm S$, and the independent sample t test was used for comparison between two groups; the skewed distribution measurement data was described by M (P_{25}, P_{75}) and the Mann-Whitney U test was used for comparison between two groups. The count data was described by a ratio or composition ratio, and the chi-square test was used for comparison between two groups. A level of $P < 0.05$ was used to indicate significance; all statistical tests were two-tailed. Binary logistic regression analysis was used before PSM while the conditional logistic regression analysis was performed with the help of Cox regression model in SPSS 24.0 to evaluate the effect of breast size on the risk of breast cancer after matching. Record a virtual survival time for each row before and after the match. The survival time was regarded as time variable, outcome was regarded as status variable, and the remained variables were regarded as covariates. The default "case group" has a short survival time, and the "control group" has a long survival time. Odds ratio of breast cancer was calculated in the highest vs lowest quartile of breast volume, as the ratio between the observed prevalences, and expressed with the 95% confidence interval.

Ethics statement

Written informed consent was obtained from all study participants and ethical approval was granted by the ethics committee of Nanfang Hospital.

Results

Data and procedures

A total of 208 cases were in the case group, and 340 cases were in the control group. The PSM process was performed by SPSS 24.0, and 185 cases were successfully matched after balancing the confounding factors of two groups of patients.

The measured bilateral breast data were averaged and calculated the breast volume useing the BREAST-V. Breast volume was regarded as a continuous variable and the only dependent variable was whether or not breast cancer was present.

Comparison of baseline data before matching between the two groups

The measurement data included in this study were not subject to normal distribution after tested. The Mann-Whitney *U* test was used for comparison between groups. The results showed that, except for age ($P = 0.668$) and BMI ($P = 0.211$), the differences of other indicators were statistically significant (age at menarche, $P = 0.000$; age at first pregnancy, $P = 0.012$; number of pregnancies, $P = 0.045$). The age at menarche in the case group was earlier than that in the control group, the age at first pregnancy was later than the control group, and the number of pregnancies was less than that of the control group. There were no significant differences in the data between the count data groups using the chi-square test(feeding mode, $P = 0.554$; history of proliferative benign breast disease, $P = 0.321$; history of oral contraceptives, $P = 0.932$; smoking, $P = 0.201$; alcohol consumption, $P = 0.121$; history of hyperthyroidism, $P = 0.589$; family history of breast cancer, $P = 0.196$)(Table 1).

Table 1
Comparison of clinical characteristics before matching data between two groups

Covariates	Control group	Case group	Test statistics	P value
age	50.4(45.0,54.0)	50.7(45.0,57.0)	U= 34589.00	0.668
BMI	23.48(21.10,25.26)	23.72(21.23,26.04)	U= 33110.50	0.211
age at menarche	14.9(13.0,16.0)	14.3(13.0,15.0)	U= 29130.00	0.000
age at first pregnancy	23.7(21.0,26.0)	24.3(22.0,26.0)	U= 30871.50	0.012
number of pregnancies	3.0(2.0,4.0)	3.0(2.0,4.0)	U= 31835.50	0.045
feeding mode			$\chi2 = 0.350$	0.554
Breastfeeding	316(92.9%)	196(94.2%)		
Non-breastfeeding	24(7.1%)	12(5.8%)		
proliferative benign breast disease			$\chi2 = 0.984$	0.321
yes	107(31.5%)	74(35.6%)		
no	233(68.5%)	134(64.4%)		
oral contraceptives			$\chi2 = 0.009$	0.923
yes	27(7.9%)	17(8.2%)		
no	313(92.1%)	191(91.8%)		
smoking			$\chi2 = 1.638$	0.201
yes	0	1(0.5%)		
no	340(100%)	207(99.5%)		
alcohol consumption			$\chi2 = 4.230$	0.121
no risk	325(95.6%)	193(92.8%)		
low risk	15(4.4%)	13(6.3%)		
high risk	0	2(1.0%)		
History of hyperthyroidism			$\chi2 = .292$	0.589
yes	9(2.6%)	4(1.9%)		

Covariates	Control group	Case group	Test statistics	P value
no	331(97.4%)	204(98.1%)		
family history			$\chi 2 = 1.673$	0.196
yes	8(2.4%)	9(4.3%)		
no	332(97.6%)	199(95.7%)		

Comparison of baseline data after matching between the two groups

There was no significant difference in the Mann-Whitney *U* test(*P* range of 0.484 to 0.983) and the chi-square test or the Fisher exact test between two groups after PSM. The baseline data between the groups reached equilibrium. (Table 2).

Table 2
Comparison of clinical characteristics after matching data between two groups

Covariates	Control group	Case group	Test statistics	P value
age	49.9(45.0,54.0)	50.5(44.0,57.0)	U= 16454.00	0.522
BMI	23.83(21.24,25.42)	23.65(21.16,26.04)	U= 17032.00	0.938
age at menarche	14.4(13.0,15.0)	14.4(13.0,15.0)	U= 16409.00	0.484
age at first pregnancy	24.3(21.0,26.0)	24.1(22.0,26.0)	U= 17101.50	0.991
number of pregnancies	3.1(2.0,4.0)	3.1(2.0,4.0)	U= 17090.50	0.983
feeding mode			-	1
breastfeeding	175(94.6%)	175(94.6%)		
non-breastfeeding	10(5.4%)	10(5.4%)		
proliferative benign breast disease			$\chi2$ = 0.106	0.745
yes	68(36.8%)	65(35.1%)		
no	117(63.2%)	120(64.9%)		
oral contraceptives			$\chi2$ = 0.492	0.483
yes	20(10.8%)	16(8.6%)		
no	165(89.2%)	169(91.4%)		
smoking			-	1
yes	0(0)	0(0)		
no	185(100.0%)	185(100.0%)		
alcohol consumption			$\chi2$ = 1.387	0.239
no risk	178(96.2%)	173(93.5%)		
low risk	7(3.8%)	12(6.5%)		
high risk	0	0		
history of hyperthyroidism	1(0.5%)	4(2.2%)	$\chi2$ = 1.825	0.177
yes	184(99.5%)	181(97.8%)		

Covariates	Control group	Case group	Test statistics	P value
no				
family history			χ2 = 1.378	0.240
yes	4(2.2%)	8(4.3%)		
no	181(97.8%)	177(95.7%)		

Relationship between breast volume and risk of breast cancer

The breast volume data before matching were tested to follow a normal distribution (*P* = 0.200 in the control group; *P* = 0.200 in the case group), and the variance was not uniform (*P* = 0.000). The Mann-Whitney *U* test using two independent samples showed significant difference (*P* = 0.014) (Table 3); Binary logistic regression analysis of breast volume showed that the risk of breast cancer was slightly higher in the breast cancer group than in the control group(*P* = 0.009, *OR* = 1.002, 95% *CI*: 1.000 ~ 1.003). The odds ratio between lowest and highest groups based on quartile groups was 1.515, however, this result is not statistically significant(*P* = 0.089)(Table 4) .

Table 3
Comparison of breast volume before PSM

Group	cases	Mean Rank	Test statistics	*P* value
Control group	340	261.44	*U* = 30919.000	0.014
Case group	208	295.85		

Table 4
Effect of 1 cm^3 increase in breast volume after PSM on breast cancer risk and odds ratio between lowest and highest groups based on quartile groups

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
BREAST-V	0.002	0.001	6.728	1	0.009	1.002	1.000	1.003
BREAST-V(1)	-0.502	0.258	3.796	1	0.051	0.605	0.366	1.003
BREAST-V(2)	-0.209	0.251	0.690	1	0.406	0.812	0.496	1.328
BREAST-V(3)	0.415	0.244	2.885	1	0.089	1.515	0.938	2.446

After PSM, the breast volume did not follow the normal distribution. There was no significant statistical difference between two groups in independent sample Mann-Whitney *U* test *(P* = 0.438) (Table 5) and in conditional logistic regression (*P* = 0.446)(Table 6).

Table 5

Comparison of breast volume after PSM

Group	cases	Mean Rank	Test statistics	P value
Control group	185	181.19	*U* = 16315.50	0.438
Case group	185	189.81		

Table 6

Effect of 1 cm^3 increase in breast volume after PSM on breast cancer risk

Covariates	Residual Chi Square	df	Sig.
age	0.471	1	0.492
BMI	0.302	1	0.583
age at menarche	0.206	1	0.650
age at first pregnancy	0.214	1	0.644
number of pregnancies	0.011	1	0.918
feeding mode	0.000	1	1.000
proliferative benign breast disease	0.111	1	0.739
oral contraceptives	0.571	1	0.450
smoking	-	0	-
alcohol consumption	1.316	1	0.251
history of hyperthyroidism	1.800	1	0.180
family history	1.600	1	0.206
BREAST-V	0.581	1	0.446

Discussion

A Chinese study showed that abortion does not increase the risk of breast cancer, and the latest meta-analysis had not found a relationship between abortion and breast cancer risk[12]. A study by Ilic et al.[28] suggested that even short pregnancies ending in abortion add to the protection against breast cancer. Therefore, the covariates of this study included only the number of pregnancies instead of the number of deliveries.

Egan et al.[29] drawn conclusion that breast size is a positive predictor of postmenopausal breast cancer limited to those who were especially lean as young women from a population-based case-control study of women aged 50 to 79 years. Williams et al.[30] deemed baseline bra cup size was the strongest predictor of breast cancer mortality. A prospective study by Kusano et al. suggested that for women with a BMI below 25 kg/m^2, those with a bra cup size of "D or larger" had a significantly higher incidence of breast cancer than women who reported "A or smaller" (covariate adjusted $HR = 1.80$; 95% $CI = 1.13–2.88$; p trend = 0.01), though this association was limited to leaner women[31]. Then some experts pointed out the shortcomings of this study, they thought that the use of cup size alone without taking rib cage circumference into account was poorly rigorous[32]. In addition, cup size labeling was not standardized and different brands of brassieres differ in their labeling of cup size for the same breast volume. Breast size as measured by self-reported bra cup size was the biggest drawback of these studies.

For the measurement of breast volume, the gold standard is the water displacement method[33]. However, its operation is complicated and it is difficult for patients to cooperate. Three-dimensional ultrasound (3-D US)[33] is a relatively close to the water replacement method, if it is not expensive and requires professional cooperation. 3D scanning is a new and more advanced method[34]. However, for women with larger breast volume, 3D scanning is not accurate[35], and the technical and cost requirements are higher. Choppin et al.[36] considered the highest accuracy of magnetic resonance imaging (MRI) scan after comparing 3D scanning, mammography, MRI, CT examination, model casting and other methods. Itsukage et al.[37] also believed that MRI is more accurate in measuring breast volume.However, it requires data analysis software and is more expensive. The breast measurement BREAST-V formula used in this study is the first unified, more effective and reliable breast volume prediction formula designed by Longo.[27] It is the most common method used by the researcher's unit and can be used for volume assessment of breasts of different sizes and is easy to operate without higher requirement for the measurement technique. The data is subjectively less affected, and it is more accurate for measuring the breast volume.

In the present study, there was no significant difference in the age between case group and control group before PSM. The reason may be that we excluded the lower age population in the process of collecting case group data, and we found that except for the unit physical examination, the age of physical examination population has a distribution of 40 to 70, which is similar to the high-risk age of onset of breast cancer. The reason for the lack of significant difference in BMI between two groups may be due to insufficient sample size, in addition does not rule out the existence of Berkson bias.

The advantage of this study is that our breast volume data was obtained from a simple and convenient method based on linear measurement of the breast; on the other hand, PSM was used to balanced potential confounding between case group and control group to ensure the comparability between two groups to a certain extent. Compared with the traditional multivariate regression model, the over-fitting was reduced to some degree since the propensity value score was applied to all the selected patients and finally matched according to the tendency value score. In the sample size, considering the problem of unsuccessful matching, the control group collected more data than the case group, which guaranteed the matching success rate to some extent.

The limitation of this study is that although the hospitals selected have a wide range of radiation, they are limited after all, and some patients with double mastectomy cannot obtain breast size data. For the exposure rate in the population can not be accurately estimated. According to a large number of purchase data analysis, women with C cups and above accounted for at least 30%. This study requires the measurer to communicate with the person being measured, blindness cannot be established, so the existence of suspected bias is not ruled out. Young women who were breastfeeding and not breastfeeding have differences in breast volume, while older women will reduce their breast volume due to fat reduction. Therefore, although this study used PSM, imbalance cannot be completely eliminated, which is one of the shortcomings of this research.

Conclusions

In this case-control study, we found a significant difference in breast volume between the case group and the control group. Regrettably, this difference disappeared after PSM. However, the effect of breast volume on the risk of breast cancer can not be ignored. It is suggested that subsequent research can be carried out with multiple centers and large sample sizes.

Abbreviations

PSM Propensity Score Matching

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The informed consent obtained from study participants was written.

Consent for publication
Informed consent was obtained from all individual participants included in the study.

Availability of data and material
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions

Chunlan Z and Yanni W analyzed and interpreted the patient data regarding the relationship breast volume and risk of breast cancer. Xiaoxia L and Xiaohong C were mainly responsible for collecting data and Xiaoxia L was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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