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Occupational risk factors and breast cancer in Beijing, China: a hospital-based case–control study

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ABSTRACT

Introduction Studies on the association between breast cancer and occupational hazards are limited, especially in China. This is the first study to explore the relationship between breast cancer and occupational hazards in Beijing, China.

Design A hospital-based case–control study.

Setting Eight local hospitals in Beijing, China.

Participants A total of 973 female participants, comprising 495 cases and 478 controls, were recruited in our study. We identified patients who underwent diagnosis for breast cancer at one of the eight local hospitals in Beijing between 1 January 2015 and 31 December 2019; controls were individuals randomly matched from the same hospital where the cases were confirmed.

Main outcome and measure Least absolute shrinkage and selection operator (LASSO) regression was used to estimate the occupational risk factors associated with breast cancer, including night shift work history and work posture.

Results In the case group, the breast cancer type was mainly invasive, which accounted for 85.66% of all the breast cancer patients. Five risk factors were included in the final LASSO model, including body mass index (BMI), marital status, menopause, night shift work history and work posture. Furthermore, these risk factors were considered for multivariate logistic regression, and the analyses suggested that the risk of breast cancer was significantly associated with higher BMI (≥28.0 kg/m^2, OR: 2.85, 95% CI: 1.29 to 6.30); married status: married (OR: 2.67, 95% CI: 1.28 to 5.56) or divorced (OR: 4.51, 95% CI: 1.84 to 11.07); menopause (OR: 6.89, 95% CI: 5.07 to 9.36); night shift work (OR: 1.53, 95% CI: 1.11 to 2.11); and maximum standing or walking, and minimal sitting (OR: 1.80, 95% CI: 1.19 to 2.73).

Conclusion Breast cancer is associated with occupational risk factors. Night shift work, especially in a standing posture, can increase the incidence of breast cancer in women in Beijing, China.

Strengths and limitations of this study

- This is the first study to evaluate the association between breast cancer and occupational risk factors in Beijing, China.
- This study used the least absolute shrinkage and selection operator logistic regression model to analyse the risk factors for breast cancer, with a better discriminatory power that significantly improved the accuracy of the research outcomes than previous studies.
- Case–control study design has a limitation, as it is prone to recall and selection biases and hinders the inference of causality.

INTRODUCTION

As per the statistics in 2020, breast cancer is the most frequently diagnosed cancer and a leading cause of cancer-related deaths worldwide.[1] Breast cancer is also the most common cancer in Chinese women, and the number of new cases of female breast cancer in 2020 ranked the first among all malignant tumours.[2] Studies suggest that primary prevention, and early diagnosis and therapies can effectively reduce the incidence and mortality in breast cancer.[3]

The risk factors for breast cancer have become the focus of research. In previous studies, we found that the increased risk of breast cancer in participants was associated with baseline characteristics (older age,[4] high body mass index (BMI), obesity or overweight, and family history of breast cancer),[5 6] reproductive factors (early menarche and late menopause)[7 8] and lifestyle (exposure to tobacco smoke and high dietary intake of fats or fatty foods).[9–12] An increasing number of studies are analysing the relationship between occupational hazards and incidence of breast cancer. Some meta-analyses found that night shift work is a risk factor for breast cancer.[13] For instance, a case–control study from Guangzhou reported that night-shift work was associated with an increased risk of breast cancer OR (95% CI): 1.34 (1.05 to 1.72).[14] Contrastingly, a case–control study from South Korea, including 1721 pairs of participants, did not observe any correlation between the two.[15] Furthermore, few

studies have found working posture and intensity of physical activity to be related to the incidence of breast cancer[16 17]; but, these were limited number of studies with smaller sample sizes, and therefore, had certain limitations and biases. Nevertheless, few studies in China have explored the occupational risk factors for breast cancer. A study in Guangzhou, China, explored the relationship between shift work at night, sleep time and nap during the day and breast cancer; however, the occupational hazards discussed were not comprehensive.[14]

The Gail *et al*'s model, a popular assessment of breast cancer risk, was originally designed to identify women at an increased risk for entry in chemoprevention trials, but it had limited discriminatory power—approximately 60% for the values of receiver-operator characteristic (ROC) curves.[18] Several other models were also developed for predicting breast cancer risk using similar indicators. In mainland China, there were only two studies (Shanghai and Nanjing) to assess risk factors for breast cancer,[19 20] which included a limited number of single nucleotide polymorphisms and some risk factors; however, these also had discriminatory power of approximately 60%, possibly due to inclusion of fewer research variables.

Therefore, we conducted this study to investigate, for the first time, the relationship between occupational hazards, such as night shift work, working posture, working hours and physical activity, and the risk of breast cancer in women in Beijing. Furthermore, we incorporated these risk factors into the least absolute shrinkage and selection operator (LASSO) logistic regression model to improve the discriminatory power, and effectively screen the risk factors for breast cancer. Additionally, we have provided a theoretical basis for early screening and treatment of breast cancer.

METHODS

Study population

A 1:1 case–control study was conducted to explore the risk factors associated with the development of breast cancer in women in Beijing, between 1 January 2015 and 31 December 2019. Cases who underwent diagnosis for breast cancer at one of the eight local hospitals in Beijing were considered for inclusion in the study. Breast cancer was confirmed based on physical examination, mammography and pathological verification. The controls were individuals matched randomly from the same hospital where the cases were confirmed. Cases who met the following criteria were included in the study: (1) female; (2) aged 20–84 years; (3) newly diagnosed with primary breast cancer and (4) resided in Beijing for at least 5 years. The inclusion criteria for women in the control group were: (1) female; (2) aged 20–84 years; (3) no medical record of breast cancer, but sought medical advice at the same hospital during the same duration and (4) resided in Beijing for at least 5 years. All patients who met the inclusion criteria and provided an informed consent were included in the study. We classified breast cancer according to the Chinese Anti-Cancer Association Guidelines for the Diagnosis and Treatment of Breast Cancer (2019 Edition).[21]

Data collection

Face-to-face interviews were conducted by trained interviewers using a standardised questionnaire in a private office. Each questionnaire required approximately 15 min. The questionnaire included basic demographic information (BMI, level of education, marital status, smoking, alcohol consumption, dinner, sleeping time per day, etc), reproduction factors (age at menarche, previous conception, abortion history, menopause, history of benign breast diseases and family history of breast cancer) and occupational risk factors (night

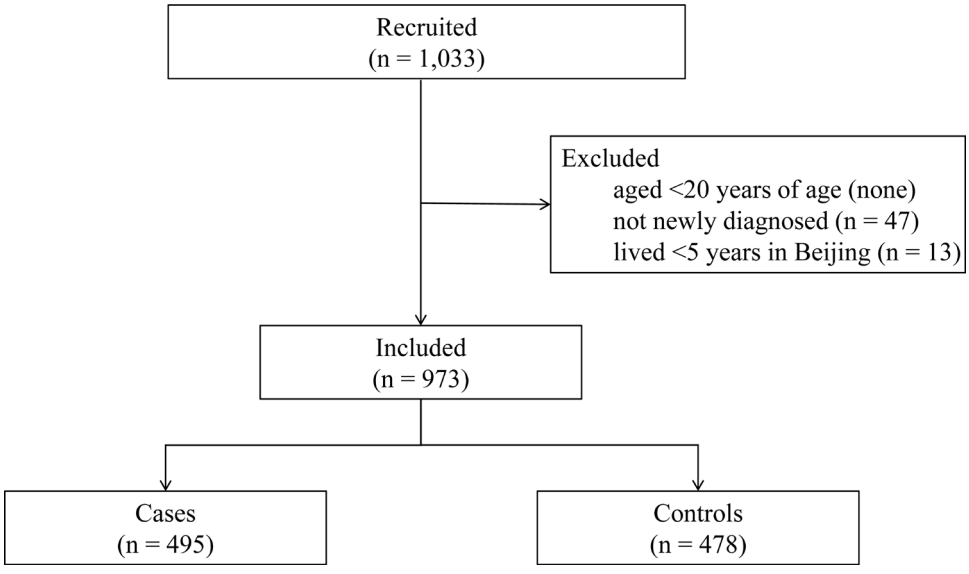

Figure 1 Study design.

Table 1 Basic characteristics

Variables	Cases n (%)	Controls n (%)	Total n (%)	P value
Total	495 (100)	478 (100)	973 (100)	
BMI (kg/m^2)				<0.001
≤18.4	24 (4.85)	37 (7.74)	61 (6.27)	
18.5–23.9	185 (37.37)	290 (60.67)	475 (48.82)	
24–27.9	202 (40.81)	128 (26.78)	330 (33.92)	
≥28.0	84 (16.97)	23 (4.81)	107 (10.10)	
Education				<0.001
<Middle school	179 (36.16)	48 (10.04)	227 (23.33)	
High school	181 (36.57)	82 (17.15)	263 (27.03)	
>University	135 (27.27)	348 (72.80)	483 (49.64)	
Marital status				<0.001
Single	10 (2.02)	66 (13.81)	76 (7.81)	
Married	435 (87.88)	387 (80.96)	822 (84.48)	
Divorced	50 (10.10)	25 (5.23)	75 (7.71)	
Smoking				0.311
Yes	13 (2.63)	8 (1.67)	21 (2.16)	
No	482 (97.37)	470 (98.33)	952 (97.84)	
Alcohol consumption				0.438
Yes	13 (2.63)	9 (1.88)	22 (2.26)	
No	482 (97.37)	469 (98.12)	951 (97.74)	
Nighttime eating				0.012
Yes	48 (9.70)	72 (15.06)	120 (12.33)	
No	447 (90.30)	406 (84.94)	853 (87.67)	
Sleeping time per day (hours)				<0.001
<22:00	189 (38.18)	104 (21.76)	293 (30.11)	
22:00–24:00	292 (58.99)	353 (73.85)	645 (66.29)	
0:00–4:00	14 (2.83)	21 (4.39)	35 (3.60)	
Oestrogen receptor status				
Negative	381 (76.97)			
Positive	114 (23.03)			
Progesterone receptor status				
Negative	358 (72.32)			
Positive	137 (27.68)			
Breast cancer type				
Non-invasive	71 (14.34)			
Invasive	424 (85.66)			
Metastasis				
Yes	121 (24.44)			
No	374 (75.56)			

shift work history, types of work shifts, years of night shift work, work posture, working hours per day, and exposure to industrial dust and high temperature at the office). BMI classification in this study is based on the Chinese Guidelines for the Prevention and Control of Overweight and Obese Adults.[22] To determine a family history of breast cancer, each participant was required to report whether her immediate relatives (father, mother or siblings) were previously diagnosed with breast cancer.

Statistical analysis

For the description of participant characteristics, variables are presented as numbers and percentages, which are compared using the χ^2 test between cases and controls. Factors with p <0.10 in univariate

Table 2 Reproductive characteristics

Variables	Cases n (%)	Controls n (%)	Total n (%)	P value
Total	495 (100)	478 (100)	973 (100)	
Age at menarche (years)				<0.001
≤12	93 (18.79)	137 (28.66)	230 (23.64)	
13	115 (23.23)	121 (25.31)	236 (24.25)	
14	121 (24.44)	119 (24.9)	240 (24.67)	
15	72 (14.55)	55 (11.51)	127 (13.05)	
≥16	94 (18.99)	46 (9.62)	140 (14.39)	
Previously conceived				<0.001
Yes	464 (93.74)	371 (77.62)	835 (85.82)	
No	31 (6.26)	107 (22.38)	138 (14.18)	
Abortion history				0.012
Yes	243 (49.09)	273 (57.11)	516 (53.03)	
No	252 (50.91)	205 (42.89)	457 (46.97)	
Menopause				<0.001
Yes	374 (75.56)	127 (26.57)	501 (51.49)	
No	121 (24.44)	351 (73.43)	472 (48.51)	
History of benign breast diseases				0.201
Yes	98 (19.80)	91 (19.04)	189 (19.42)	
No	360 (72.73)	364 (76.15)	724 (74.41)	
Unknown	37 (7.47)	23 (4.81)	60 (6.17)	
Family history of breast cancer				0.025
Yes	44 (8.89)	24 (5.02)	68 (6.99)	
No	441 (89.09)	442 (92.47)	883 (90.75)	
Unknown	10 (2.02)	12 (2.51)	22 (2.26)	

analysis were included in the LASSO model. Analyses with LASSO model were performed to select potential predictors to be used by shrinking the coefficients toward zero by setting a constraint on the sum of the absolute standardised coefficients. Shrinkage estimates with LASSO provided an important way for adjusting model's overfitting. Finally, the risk factors selected by LASSO model were analysed by non-conditional multivariate logistic regression that reports p values, OR and 95% CIs. All analyses were performed using the SAS software V.9.4. Results with two-sided p <0.05 were considered to be statistically significant.

Patient and public involvement

Patients and the public were not involved in the design or execution of this study.

RESULTS

Overall, 1033 participants were recruited in the study with a response rate of 94.86% (1033/1089). Sixty women were excluded from the study as they failed to meet the inclusion criteria. Therefore, 973 participants, including 495 cases and 478 controls, with response rates of 93.73% (495/528) and 95.41% (478/501), respectively, were considered for the final analysis. The detailed information is presented in figure 1.

Basic characteristics of cases and controls

Women with breast cancer had a higher BMI (24.0–27.9 kg/m^2 in 40.81% and ≥28.0 kg/m^2 in 16.97% cases, p<0.001), and >30% had a middle school level education or below (p<0.001) than that in controls (table 1).

Reproductive characteristics of cases and controls

As shown in table 2, increased number of cases with breast cancer had delayed menarche (age ≥16 years in 18.99%, p<0.001), conceived (93.74%, p<0.001), reached menopause (75.56%, p<0.001) and a family history of breast cancer (8.89%, p=0.054) than that in controls.

Comparison of occupational risk factors in cases and controls

As shown in table 3, >30% of the participants had night shift work history. Rotating night shift was the frequent type of work shift, and accounted for 21.27%. Majority of the times sitting, and sometimes standing or walking, was

Table 3 Occupational risk factors

Variables	Cases n (%)	Controls n (%)	Total n (%)	P value
Total				
Night shift work history				0.001
Yes	122 (24.65)	172 (35.98)	294 (30.22)	
No	373 (75.35)	306 (64.02)	679 (69.78)	
Types of shift work				<0.001
Permanent night shift	4 (0.81)	2 (0.42)	6 (0.62)	
Rotating night shift	79 (15.96)	128 (26.78)	207 (21.27)	
Irregular night shift	39 (7.88)	42 (8.79)	81 (8.32)	
No	373 (75.35)	306 (64.02)	679 (69.78)	
Years of night shift work				<0.001
≤1	8 (1.62)	14 (2.93)	22 (2.26)	
2–5	37 (7.47)	52 (10.88)	89 (9.15)	
6–10	28 (5.66)	52 (10.88)	80 (8.22)	
≥11	49 (9.90)	54 (10.48)	103 (10.59)	
No	373 (75.35)	306 (64.02)	679 (69.78)	
Work posture				<0.001
Majority sitting, and sometimes standing or walking	264 (53.33)	313 (65.48)	577 (59.30)	
Comparable sitting and standing	118 (23.84)	104 (21.76)	222 (22.82)	
Majority standing or walking, and sometimes sitting	113 (22.83)	61 (12.76)	174 (17.88)	
Working hours per day				0.191
<2	24 (4.85)	9 (1.88)	33 (3.39)	
2–4	30 (6.06)	20 (4.18)	50 (5.14)	
5–7	131 (26.46)	157 (32.85)	288 (29.6)	
≥8	310 (62.63)	292 (61.09)	602 (61.87)	
Industrial dust				0.001
Yes	450 (90.91)	460 (96.23)	910 (93.53)	
No	45 (9.09)	18 (3.77)	63 (6.47)	
High temperature at the office				0.003
Yes	467 (94.34)	469 (98.12)	936 (96.20)	
No	28 (5.66)	9 (1.88)	37 (3.80)	

the frequent work posture, and accounted for 59.30%. More than 90% of the participants had industrial dust (93.53%) and high temperature (96.20%) exposure history.

Risk factors for breast cancer by LASSO selection and multivariate logistic regression analysis

Five risk factors, including BMI, marital status, menopause, night shift work history and work posture, were finally included in the LASSO model. Furthermore, these risk factors were selected for multivariate logistic regression. The analyses indicated that the incidence of breast cancer significantly associated with higher BMI (≥28.0 kg/m^2, OR: 2.85, 95% CI: 1.29 to 6.30), married (OR: 2.67, 95% CI: 1.28 to 5.56) or divorced (OR: 4.51, 95% CI: 1.84 to 11.07) marital status, menopause (OR: 6.89, 95% CI: 5.07 to 9.36), night shift work (OR: 1.53, 95% CI: 1.11 to 2.11) and majority standing or walking and sometimes sitting posture (OR: 1.80, 95% CI: 1.19 to 2.73) (table 4).

Accuracy of model

The accuracy of the logistic model was determined by the ROC curves, with an area under the curve of 0.8691. The detailed information is shown in figure 2.

DISCUSSION

In this case–control study, we found the incidence of breast cancer to be closely related to occupational hazards. Majority of the participants with a history of night shift work and who worked in standing posture had an increased risk of breast cancer. Additionally, we found that some baseline demographic characteristics, such as

Table 4 Multivariate logistic regression analyses for risk factors for breast cancer

Variables	P value	OR	95% CI
BMI (kg/m^2)			
≤18.4		1.00	
18.4–23.9	0.212	0.67	0.35 to 1.26
24.0–27.9	0.405	1.32	0.69 to 2.55
≥28.0	0.010	2.85	1.29 to 6.30
Marital status			
Single		1.00	
Married	0.009	2.67	1.28 to 5.56
Divorced	0.001	4.51	1.84 to 11.07
Menopause			
Yes	<0.001	6.89	5.07 to 9.36
No		1.00	
Night shift work history			
Yes	0.010	1.53	1.11 to 2.11
No		1.00	
Work posture			
Majority sitting, and sometimes standing or walking		1.00	
Comparable sitting and standing	0.878	1.03	0.71 to 1.49
Majority standing or walking, and sometimes sitting	0.005	1.80	1.19 to 2.73

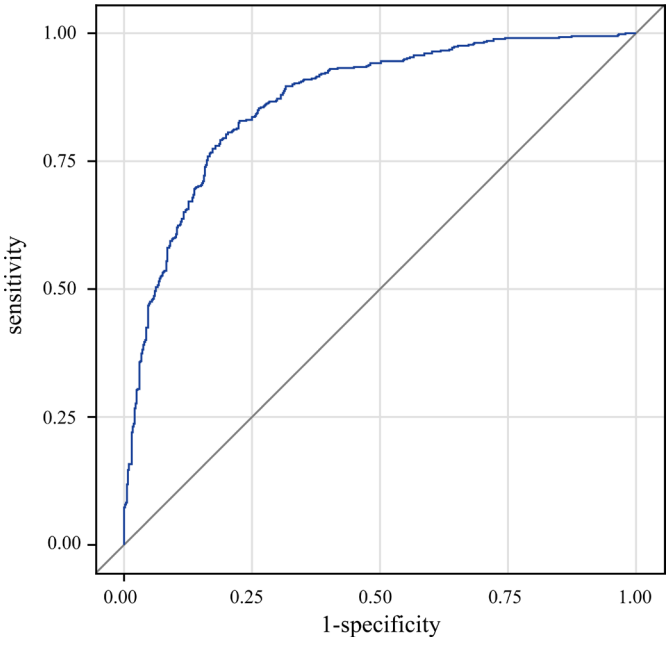

Figure 2 Accuracy of model analysis using receiver-operator characteristic.

obesity (BMI ≥28 kg/m^2), married or divorced marital status, and menopause were also risk factors for breast cancer.

We found 1.53-times increased incidence of breast cancer in individuals with a history of night shift work that in those with no such history. The possible mechanism could be that night shift work disrupts the circadian rhythm and contributes to an increased risk of breast cancer. Studies have shown that changes in the circadian rhythm inhibit the secretion of melatonin that stimulates secretion of oestrogen, changes the functions of oestrogen receptors and inhibits the activation of tumour antiproliferative mechanisms, and thus, increases the risk of breast cancer in women.[23] It is indicated that immunohistochemical indicators are closely linked to breast cancer. Furthermore, a study has indicated that epigenetic regulation of *CLOCK*, *BMAL1*, *CRY1* and *PER1* may contribute to incidence of breast cancer in shift workers.[24] Moreover, telomere shortening associated with the duration and intensity of night work is also a risk factor for breast cancer in women.[25] Several studies have also indicated that night shift work is a risk factor for breast cancer.[26–28] Therefore, considering the significantly higher risk of breast cancer in people working at night, the government should implement prophylactic treatment for cancers. Additionally, it is necessary to limit night shift work in women with the highest risk of developing breast cancer, and comply with appropriate number of breaks and ergonomic working conditions.

Furthermore, we found that working postures, such as standing or walking, also increased the risk of breast cancer. A majority of the workers working in standing position performed heavy physical activity than those working in sitting position. Previous studies have showed that many diseases are related to the immune function of the body.[29] A moderate physical activity can increase the number of natural killer cells, lymphocytes, macrophages and monocytes, and, therefore, enhance the immune function in the body and reduce the occurrence of breast cancer. However, heavy physical activity reduces immune function. An epidemiological survey based in Africa showed that incidence of breast cancer is not reduced by high-intensity physical activity.[30] Moreover, a population-based prospective cohort study found that occupational sedentariness was associated with increased breast cancer risk.[31] Therefore, avoiding standing for long durations and ensuring a reasonable schedule of work and rest will help reduce the incidence of breast cancer.

Studies found that obesity can significantly increase the risk of breast cancer. The World Cancer Research Foundation suggests that obesity is a risk factor for breast cancer.[32 33] In obese women, adipocytokine disorders, insulin and insulin-like growth factor system disorders, and abnormally increased oestrogen levels can increase the risk of breast cancer.[34 35] A large-scale prospective study of 162 691 postmenopausal women in the UK indicated a positive correlation between obesity in postmenopausal women and risk of breast cancer.[36] A prospective cohort

study of 3.5 million in Spain also reported that postmenopausal women have an increased risk of breast cancer.[37] However, the relationship between obesity in premenopausal women and risk of breast cancer is not validated and needs further study.[38 39] Therefore, the prevalence of overweight and obesity should be reduced by changing lifestyles and adopting reasonable diet to reduce the incidence of breast cancer.

Compared with the incidence in unmarried women, married or divorced women showed an increased risk of breast cancer. Married or divorced women may face greater mental stress, such as work–family conflicts, grievances, etc. Long-term psychological depression and accumulation of negative energy may worsen the sickness. Therefore, an optimistic attitude, and adopting methods to combat stress and eliminate negative emotions, can help prevent the occurrence of breast cancer. We also found that menopausal status is a high-risk factor for breast cancer than non-menopausal status. It may be that menopausal women are older, more likely to develop breast cancer[40 41] and more likely to receive menopausal hormone therapy.[42] Moreover, a meta-analysis of 58 studies showed that the risk of breast cancer increases by 15%–29% after receiving menopausal hormone therapy.[43] Therefore, postmenopausal women should take hormone therapy as little as possible to reduce the incidence of breast cancer.

A major advantage of this study is that it explores the relationship between occupational hazards and breast cancer based on a hospital case–control study. For the first time, eight medical institutions were randomly selected in Beijing, and a questionnaire survey was conducted in the form of one-to-one interviews. Additionally, this study used the LASSO logistic regression model to analyse the risk factors for breast cancer, with a discriminatory power of approximately 80% that significantly improved the accuracy of the research outcomes than that with discriminatory power of 60% reported in a previous study.[44] However, the limitations of the study should be mentioned. First, this is a case–control study and is prone to recall and selection biases. Nevertheless, we selected patients who were diagnosed with breast cancer for the first time in the past 5 years and trained investigators to minimise recall bias. Moreover, the control and case groups were selected from the same medical institution to minimise the selection bias. Second, we only investigated breast cancer patients in eight medical institutions in Beijing, which has certain limitations. However, according to the sample size calculation formula, the number of people surveyed in this research has met the requirements, and the research results are relatively stable. Third, we did not mention the age of the respondent in the questionnaire; this needs to be investigated in future studies. Fourth, further research is needed to explore average number of night days, the age at which the participants started performing night shifts, working posture and the relationship between obesity, interaction of physical activity and breast cancer, and obesity and breast cancer in women with different menopausal status.

In conclusion, findings of the present study indicated that night shift work and a standing or walking work posture were associated with a risk of breast cancer. We suggest that national awareness campaigns that aim to limit night shift work in women with the highest risk of developing breast cancer, avoiding standing for a long duration, and ensuring a reasonable schedule of work and rest, could be implemented to reduce the incidence of breast cancer in China.

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Contributors AL wrote the main manuscript text and analysed the data. ZShen and YY conducted the analysis and contributed to study design. ZSun, SY, XT and ZH contributed to data collection. GY, LH and ZW helped to review the manuscript outline and suggested revisions. All authors have reviewed the manuscript and approved the submitted version. YY was responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval The study protocol was reviewed and approved by the Institutional Review Board of the Beijing Center for Disease Control and Prevention (IRB #201920).

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