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Impact of Traditional Chinese Medicine Constitution on Breast Cancer Incidence: A Case-Control and Cross-Sectional Study

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ABSTRACT

The term "Constitution of Traditional Chinese Medicine" refers to the physical and psychological characteristics of the body remaining constant. Unbalanced TCMCs make people more susceptible to illness. To evaluate the effectiveness of TCMCs, this study examined how Chinese healthy women and breast cancer patients were disseminated in Hong Kong. To analyze the physical constitution scale in TCM and identify the TCMC categories, 305 healthy women and 305 BC women were recruited for the study. Questionnaires were used to prepare the sociodemographic information and related BC risk factors. Multiple-factor analysis was used to identify the relationship between BC and imbalanced TCMC forms. Compared to healthy individuals, BC patients had a significantly higher percentage of unbalanced TCMC, in particular, qi-depressed, Yin-deficiency, blood stasis, qi-deficiency, and wetness-heat ($P < 0.05$). According to the results of the stepwise logistic regression analysis, there was a positive correlation between qi-depressed and BC (CI = 1.49-6.92; OR = 3.21). The link significantly increased when qi-depressed constitutions were combined with wetness-heat (CI = 1.83-12.71; OR = 4.82) or blood-stasis (CI = 1.31-8.16; OR = 3.27). BC was associated with both constitutions (CI = 1.02-8.17; OR = 2.88). The qi-depressed's constitution was a risk factor for BC on its own. Similarly, when combined with qi-depressed, the constitutions of the blood-stasis and wetness-heat may also play important roles in the incidence of BC. This result raises the prospect that individuals with BC vulnerabilities may exhibit inconsistent unbalanced TCMC types, suggesting that Chinese constitutional analysis could be a viable method for identifying BC-vulnerable populations and the consequent inhibition of BC.

Keywords: TCMC, Etiology, BC, Pathogenesis, Correlation

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Introduction

Breast cancer (BC), the leading cause of malignant death worldwide, is one of the most prevalent tumors in women [1-3]. To increase the survival rate of BC patients, several novel diagnoses and therapies have been proposed [4]. Western medicine, however, was unable to provide a medical "antidote" for BC because of its higher prevalence. Despite receiving standard therapies, about 10–30% of people with BC develop metastases and recurrence. Within five years, the majority of instances may decline [5]. For both doctors and BC patients, identifying risk factors and preventative interventions is crucial. Obesity, radiation, family history, alcohol consumption, physical activity, hormonal changes, and environmental factors are high-risk factors and contributors to the incidence of BC, according to several epidemiological and clinical studies conducted in previous decades [6-14]. Some factors, such as age and family history, are outside the scope of medical professionals; others, including smoking and eating habits, are still controversial and unconvincing [15-18], and the underlying mechanisms are not entirely

clear. As a result, modern medicine is still unable to shed light on the causes and efficient prevention of BC. Based on the TCM constitution (TCMC), it is acceptable and inevitable to learn about the etiology and pathogenesis of BC because genetics and environmental factors play a significant role in its development. In other words, the link between TCMC and BC incidence is a reasonable alternative for investigating the etiology and inhibition of BC as indicated in TCM's systematic method.

The physical and psychological characteristics of the human body remain constant, as indicated by TCMC [19]. A person's constitution is shaped by their environment, lifestyle, and genetic traits, among other things [20]. Blood-stasis, qi-depressed, qi-deficiency, phlegm-wetness, Yang-deficiency, wetness-heat, Yin-deficiency, many subclasses, and imbalanced (biassed) are the two main categories into which TCMC is typically categorized [21]. In contrast to biassed constitutions, which usually disclose an unstable or distressed healthy state, balanced constitutions indicate a whole state of health, making people more prone to various disorders. Additionally, several clinical studies have confirmed the variations in the prevalence and constitutional characteristics of numerous diseases. For example, compared to other constitutional kinds, those with phlegm-wetness are more likely to develop hyperlipidemia and coronary heart disease [20, 21].

In the recent decade, limited clinical data on several forms of TCMC that are prone to promoting the development of BC have become available [22-26]. Unfortunately, all studies featured constraints such as sample size, predefined inclusion/exclusion criteria, a healthy control group, and so forth. As a result, no firm clinical judgments were made, and it was still unclear what the TCMC kinds and BC meant. Therefore, the current study was designed to track the spread of BC among various TCMC groups, investigate the possibility that biassed TCMC is the primary risk factor for the development of BC, and establish a link between biassed TCMC types and factors that are prone to BC development.

Materials and Methods

A cross-sectional, retrospective, and case-control study was employed in the present investigation. The recruitment of patients with BC was employed through advertisements on websites, newspapers, and radios, and their data was obtained by face-to-face consultation at the School of Chinese Medicine, University of Hong Kong, from March 2018 to December 2019. The healthy individuals were randomly chosen from the wide populations in Hong Kong.

Inclusion criteria

The inclusion criteria include

1. Local Chinese women
2. BC was detected using biopsy within a year
3. Age of more than 20 years
4. Agreed the informed content
5. Residential in Hong Kong for > 3 years before the BC diagnosis.

Exclusion criteria

The exclusion criteria include

1. Individuals with a neurological disorder, psychological disorder
2. Patients with other classes of malignancy or other physical illnesses.
3. Those who did not finish the informed consent or questionnaires.

Both criteria for healthy women in the present survey include

1. No analysis of BC, breast, or gynecologic illnesses
2. No consultation with any doctor for any complaint during 90 days.
3. Other inclusion/exclusion criteria were indistinguishable from those accepted for employing patients with BC.

Protocol for the investigation

The ethical endorsement was achieved by the University Research Ethics Board, University of Hong Kong (Ethical number: UW 12-010). Based on the Clinics and workshops, participants were chosen and given a brief

outline of the TCMC study. Participants were asked to fill out a written informed consent followed by the data collected through a self-administered questionnaire.

The following three steps were undertaken to confirm the value of the investigation. First, participants were examined using the same standard procedures to confirm the reliability and uniformity of the survey. Secondly, the questionnaire was cautiously checked and absent items were immediately omitted. Thirdly, data entry was carried out then and there via Epidata version 3.1 (EpiData-Association, 2006) and was statistically analyzed into SPSS version 22 (SPSS Inc., Chicago, IL).

Investigation of the content

All contents were itemized in a questionnaire comprised of 3 parts.

1. Socio-demographic data: age, job status, educational qualification, height and weight, marital status
2. Risk factors of BC: History of the family, reproductive, and breastfeeding; the age of menarche and menopause, smoking, alcohol intake, hormonal contraception, and HRT, the habit of physical exercise at least once time for every week.
3. TCM Physical Constitution Scale: it was established by Prof. Wang and validated by former investigations [23, 26]. In this study, we employed slight modifications in the TCMC Scale. Based on its standard and TCMC types, it has been employed by many professionals and researchers that are endorsed by the Association of Chinese Medicine in China to determine an individual's TCMC [25]. The scale generally comprises 60 variable items scored on a five-point scale, that ranges from 1 (not at all) to 5 (very much) and has 9 subscales that measure the individual TCMC type (i.e., blood-stasis, phlegm-wetness, qi-deficiency, qi-depressed, wetness-heat, Yin-deficiency, Yang-deficiency, and inherited special constitution). An individual type of constitution and the total score was calculated [27].

Apart from the three main parts in the questionnaire, additional data on the disease characteristics were also included: affected site, clinical stage, metastasis status, molecular subtype, and time of disease onset.

Data analysis

The descriptive method was used for the statistical analysis of data. The chi-square test or independent t-test was used for the analysis of each risk factor, TCMC type, patients with variable clinical stages, molecular subtypes, and BC with $P < 0.25$ in univariate analysis [23]. All tests were performed using two-tailed with $P < 0.05$.

Results and Discussion

Characteristics of BC patients

The response rate was 87% since 472 BC patients took part, and 61 of them declined to complete the questionnaires because they were illiterate. 96 individuals out of 411 were excluded because they had not lived in Hong Kong for the previous three years (n = 9), had a diagnosis made a year prior (n = 66), had other illnesses (n = 36), had hepatic/renal failure (n = 6), or had psychological issues (n = 17). As a result, 305 patients in total filled out the questionnaires, which were then submitted for analysis.

About 1136 people took part in the healthy individual screening; 40 were turned away for not completing the questionnaire, therefore the response rate was 96%. The following patients were excluded from 1096: those who did not reside in Hong Kong (n = 23), those who had metabolic or nutritional disorders (n = 110), those who had breast or gynecological diseases (n = 312), those who had other illnesses (n = 261), those who had psychological disorders (n = 91), and those who had recently visited the hospital (n = 567). A total of 389 healthy people were therefore examined, and 305 women were selected for further investigation based on their age (45–55 years), level of education (upper secondary or higher education), and occupation (full-time job). Between the BC patients and the healthy participants, there was no discernible difference **(Figure 1; Table 1)**.

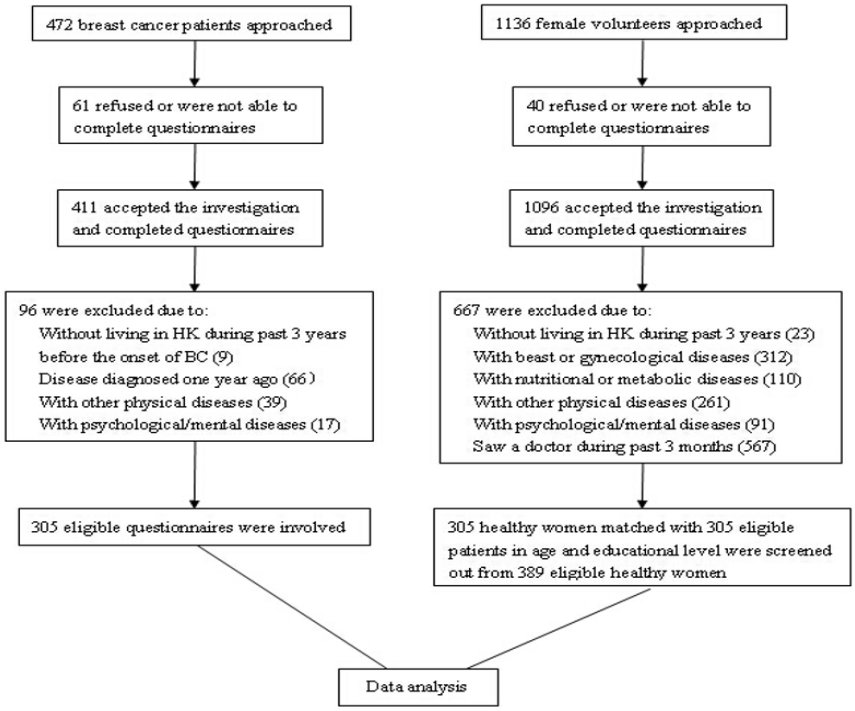

Figure 1. The flow of study participants

Table 1. The distribution of study based on age, education, occupation, and religion

	Healthy (n = 305)		**Patients with BC (n = 305)**		**P-value**
	N	**%**	**N**	**%**	
Age (years)					0.840
≤ 44	67	22.0	69	22.6	
45～55	166	54.4	159	52.1	
≥ 56	72	23.6	77	25.2	
Min	31		31		
Max	77		79		
Mean ± SD	50.45 ± 7.67		50.52 ± 7.83		0.904$^{\Psi}$
Education					0.743
Primary school	19	6.2	26	8.5	
Lower secondary	58	19.0	60	19.7	
Upper secondary	128	42.0	116	38.0	
Under-graduate	62	20.3	67	22.0	
Postgraduate or above	38	12.5	36	11.8	
Occupation					0.289
Full-time job	182	59.7	179	58.7	
Part-time job	23	7.5	34	11.1	
Housewife/no job	100	32.8	92	30.2	
Working nature					0.594
Mental	155	51.7	147	51.8	
Manual	125	41.7	112	39.4	
Both	20	6.7	25	8.8	
Religious status					0.932
Yes	106	34.8	105	34.4	
No	199	65.2	200	65.6	

The P-value noticeable with $^{\Psi}$ is from the student t-test and the others obtained from the chi-square test.

Characteristic features of the illness

Figure 2 displays the traits and attributes of the illnesses. Individuals were evaluated for Her2 overexpression (14.8%), Luminal A (47.2%), Luminal B (16.7%), Triple-Negative (16.1%), unilateral cancer (97.7%), and staged from I to III (83.9%). More than 40% of patients experienced cancer metastases, with 38.3% of those cases involving lymph nodes.

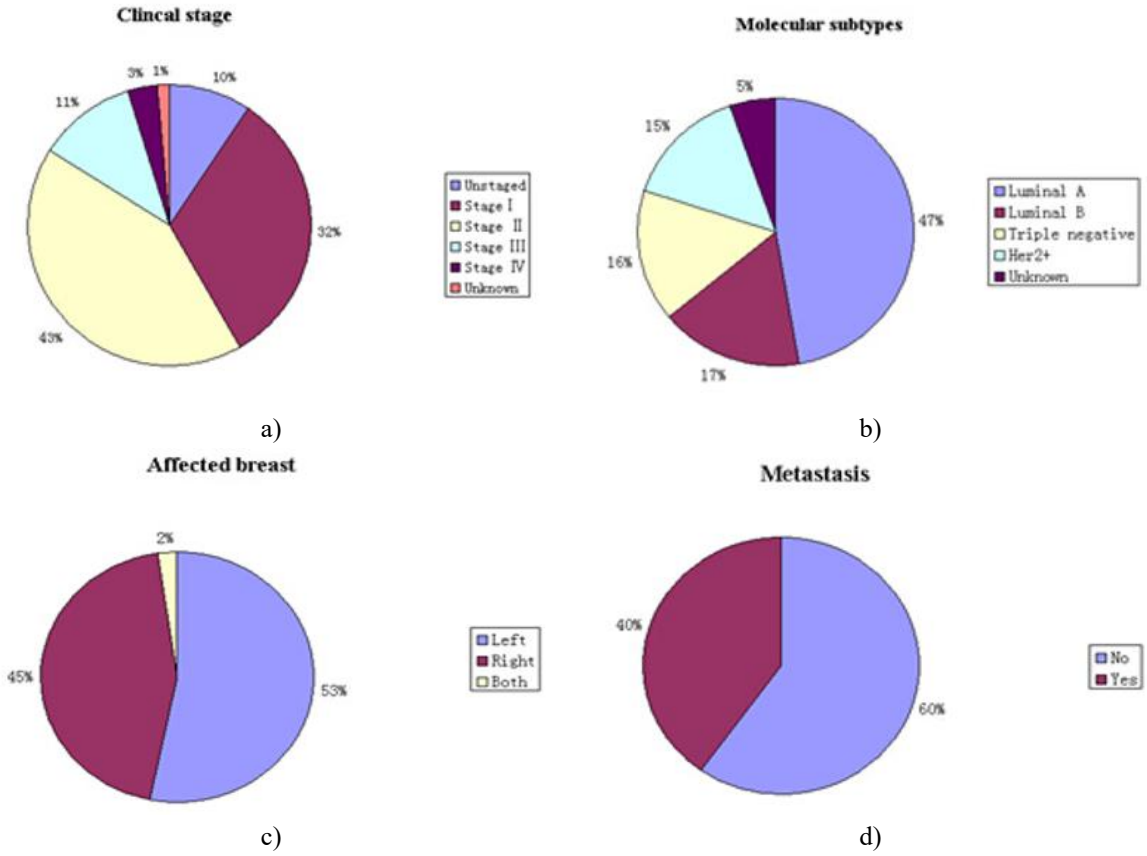

Figure 2. Disease characteristics of the studied patients with BC

Risk factors

Table 2 lists the common risk factors for BC. The distribution of family history and exercise habits was significantly different between BC patients and healthy people ($P < 0.001$). On the other hand, there were no discernible variations in menarche age, emotional state, reproductive status, or hormone use ($P > 0.5$). Other characteristics like marital status, age, smoking, BMI, pregnancy, nursing, and alcohol use did not show any significant differences either ($P = 0.129–0.407$).

Table 2. Distribution of common risk factors of patients with BC and healthy individuals

	Patients with BC (n = 305)	**Healthy individuals (n = 305)**	**P-value**
Basal metabolic index			0.273
< 18.5	18 (5.9%)	26 (8.6%)	
18.5～24.9	221 (72.9%)	229 (75.6%)	
25～27	34 (11.2%)	26 (8.6%)	
> 27	30 (9.9%)	22 (7.3%)	
Smoking			0.363
No	293 (96.1%)	297 (97.4%)	
Yes	12 (3.9%)	8 (2.6%)	
Alcohol use			0.143
No	247 (88.5%)	259 (92.8%)	

Yes	32 (11.5%)	20 (7.2%)	
Marital status			0.156
Single	58 (19.0%)	58 (19.0%)	
Cohabitating/Married	224 (73.4%)	210 (68.9%)	
Windowed/Divorced	23 (7.5%)	37 (12.1%)	
Reproductive status			0.532
Never	92 (30.2%)	85 (27.9%)	
Yes	213 (69.8%)	220 (72.1%)	
Parity			0.907
0	93 (30.5%)	87 (28.5%)	
1	79 (25.9%)	76 (24.9%)	
2	104 (34.1%)	111 (36.4%)	
≥ 3	29 (9.5%)	31 (10.2%)	
Breastfeeding			0.407
Never	192 (63.0%)	177 (58.0%)	
≤ 1 month	54 (17.7%)	57 (18.7%)	
> 1 month	59 (19.3%)	71 (23.3%)	
Age at menarche (yrs)			0.792
< 12	43 (14.1%)	45 (14.9%)	
≥ 12	262 (85.9%)	258 (85.1%)	
Age at first full-time pregnancy (yrs)			0.129
< 30	123 (58.6%)	140 (65.7%)	
≥ 30	87 (41.4%)	73 (34.3%)	
Emotional status			0.637
happy	108 (35.4%)	120 (39.3%)	
Ordinary	111 (36.4%)	104 (34.1%)	
Blank	52 (17.0%)	54 (17.7%)	
Unhappy (ever)	34 (11.1%)	27 (8.9%)	
Family history of BC			<0.001
No	249 (81.6%)	284 (93.1%)	
Yes	56 (18.4%)	21 (6.9%)	
hormone replacement therapy/oral contraceptive use			0.833
No	251 (82.3%)	249 (81.6%)	
Yes	54 (17.7%)	56 (18.4%)	
Exercise regularly			< 0.001
No	257 (84.3%)	154 (50.5%)	
Yes	48 (15.7%)	151 (49.5%)	
Exercise duration(yrs)			0.034
< 3	15 (34.9%)	36 (25.5%)	
3-5	16 (37.2%)	31 (22.0%)	
6-10	3 (7.0%)	12 (8.5%)	
> 10	9 (20.9%)	62 (44.0%)	
Family history of other kinds of cancers			< 0.001
No	174 (57.0%)	222 (72.8%)	
Yes	131 (43.0%)	83 (27.2%)	

P-value obtained from chi-square test.

Types of TCMC

Figure 3 shows the distribution of each TCMC type and the proportion that corresponded to it in both healthy women and BC patients. Among healthy individuals, the most prevalent types of TCMC were Qi-deficiency (38.4%) and Yang-deficiency (31.5%), while Qi-depressed constitutions were the intermittent kind (19%). In contrast, Qi-deficient (47.9%) and Qi-depressed (43.9%) constitutions were observed in BC patients. Additionally, compared to healthy people, patients with BC had a noticeably higher prevalence of biassed constitutions. The frequency of Yin-deficiency and Qi-depressed constitutions was also highly significant ($P < 0.01$), and there were substantial differences ($P < 0.05$) between the two groups in terms of qi-deficiency and wetness-heat constitutions. Normality constitution was found in both BC patients (24.3%) and healthy individuals (29.2%), however, there was no significant difference between the two. Additionally, no significant differences between patients with various molecular subtypes and clinical stages were found.

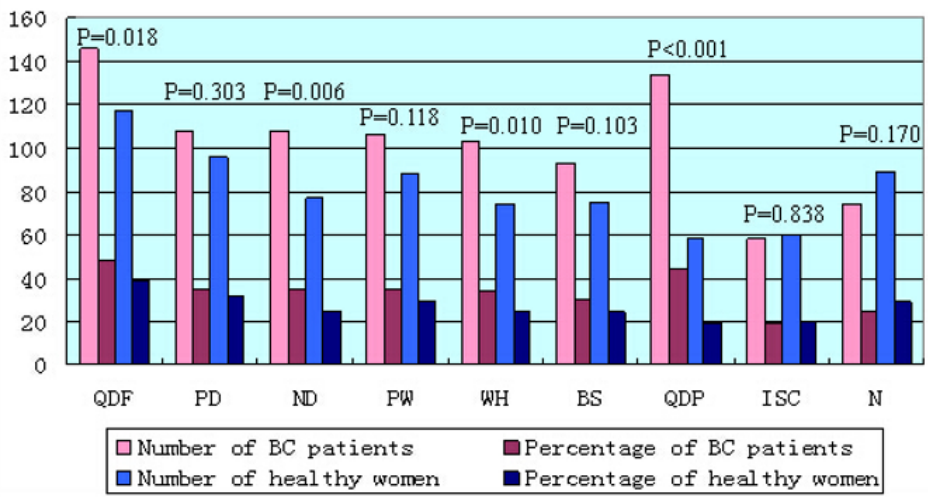

Figure 3. Distribution of TCMC types among the participants (N, %)

Abbreviations: QDF, qi-deficiency constitution; PD, Yang-deficiency constitution; ND, Yin-deficiency constitution; PW, phlegm-wetness constitution; WH, wetness-heat; BS, blood-stasis constitution; QDP, qi-depressed constitution; ISC, inherited special constitution; N, normality constitution

TCMC types and other factors connected to the incidence of BC

To identify vulnerable biassed TCMC types, stepwise logistic analysis, and the statistical Chi-square test were utilized as candidate variables **(Table 3)**. There was a strong correlation between Qi-depressed and physical exercise constitution in BC, suggesting that Qi-depressed may be a risk factor in and of itself. In a similar vein, we employed the combined constitutions of two biassed TCMC types as a candidate variable to identify two biassed TCMC types and determine their effects using 15 stepwise logistic regression models. According to the findings, only coupled constitutions, such as Qi-depressed joint with Wetness-heat (Model 2), Qi-depressed joint with Blood-stasis (Model 3), and Wetness-heat combined with Blood-stasis (Model 4), were significantly connected to BC.

Table 3. Relationship between BC and associated factors (based on stepwise logistic regression)

Variable	OR	SE	95% CI	p-value
Model 1: Involved factors: Each biased TCMC type and each BC risk factor ($P < 0.25$)				
Chi-square = 15.53 (2 df), log-likelihood = 184.56, $P < 0.01$				
QDP	3.21	0.39	1.49-6.92	0.003
Exercise duration	0.74	0.15	0.55-0.99	0.043
Model 2: Involved factors: Each BC risk factor, and combined constitutions of qi-depressed and wetness-heat and other biased types ($P < 0.25$)				
Chi-square = 16.97(2 df), log-likelihood = 183.11, $P < 0.001$				
QDP+WH	4.82	0.50	1.83-12.71	0.001
Exercise duration	0.74	0.15	0.55-0.99	0.044
Model 3: Involved factors: Each BC risk factor, and combined constitutions of blood-stasis and qi-depressed and other biased types ($P < 0.25$)				

Chi-square = 13.14(2 df), log-likelihood = 186.95, P = 0.001				
QDP+BS	3.27	0.47	1.31-8.16	0.011
Exercise duration	0.70	0.15	0.52-0.93	0.014
Model 4: Involved factors: Each BC risk factor, and combined constitutions of Blood-stasis and Wetness-heat and other biased types (P < 0.25)				
Chi-square = 19.41(3 df), log-likelihood = 180.68, P < 0.001				
WH+BS	2.88	0.53	1.02-8.17	0.047
QDP	2.38	0.43	1.03-5.49	0.042
Exercise duration	0.73	0.15	0.54-0.99	0.042

TCMC details the individual's serious medical issues as well as his general state of health. Moreover, TCMC describes its susceptibility and potential to detect specific diseases [28]. As a result, TCMC is recognized as having the potential to be used in disease defense and prevention by rectifying biassed TCMC and re-establishing a new, balanced TCMC. The pathologic progression, disease onset, and individual characteristics can all be identified and corrected with the use of balanced TCMC. In recent years, TCM practitioners and researchers have become more interested in the link between TCMC and certain disorders [29]. Additionally, the current study provides a limited survey insight into the forms of TCMC in BC patients. Notably, this is a preliminary study that assesses the impact of biassed TCMC on the incidence of BC using a case-control design. Researchers and TCM experts may find this decision-useful in better understanding the connection between the incidence of BC and biassed TCMC, and the study's findings may serve as a potential reference for those delegates to support effective illness inhibition and treatment.

We identified the biassed TCMC categories associated with the beginning of BC progression in the current investigation. The distribution of biassed TCMC types was significantly different from that of the healthy person. The constitution of Qi-depressed was determined to be significant at 3.21 (CI = 1.49-6.92), indicating that it can function as a key independent risk factor for BC. The stepwise logistic regression validated the common risk variables of BC.

Furthermore, candidate variables show that the combined constitutions of qi-depressed and blood-stasis have a somewhat larger OR value (OR = 3.27, CI = 1.31-8.16), which is fairly significant; still, both combined constitutions raise the risk of BC. Similarly, the Wetness-heat and qi-depressed constitutions appear as variables, with the latter showing a somewhat larger OR of 4.82 (CI = 1.83-12.71), suggesting that the Wetness-heat constitutions may have a stronger superposition effect and increase the threat of BC.

Additionally, the threat of BC may be increased by the combination of the Blood-stasis and Wetness-heat constitutions (CI = 1.02-8.17, OR = 2.88). The results confirm that there is a high correlation between the occurrence of BC and the constitutions of blood stasis, wetness-heat, and qi-depressed. Nevertheless, the threat posed by BC was not increased by the separate constitutions of blood-stasis and wetness-heat. However, the qi-depressed's constitution can independently increase BC's threat. The threat of BC progression is increased by the coupled constitutions or qi-depressed, which confirms a spectacular superposition influence.

The primary pathological marker of liver-qi stagnation is the constitution of qi-depressed, which is typified by symptoms such as anxiety, depression, melancholy, hypochondriac fullness, irritability, insomnia, and sighing [27]. According to TCM belief, one of the causes of BC development is liver-qi stagnation [30]. The reason for TCM's attention to this issue is demonstrated by our results, which also support previous research showing that constitution qi-depressed is an independent triggering factor for BC advancement.

However, it is noted that some clinical indicators of a qi-depressed constitution are very similar to the symptoms of psychological diseases, which are usually associated with an emotional life that is not fulfilling. There is some discrepancy between the composition of qi-depressed in TCM and psychological disorders in Western medicine [31]. In contrast to the constitution of qi-depressed, which is characterized by both psychological and physiological dysfunctions, including hypochondriac and chest fullness, as well as throat barricade sensation, the primary cause is the symptoms of psychological illnesses, which include emotional abnormalities and mood disorders [32]. Hence, qi-depressed constitutions could not be quantified as the symptoms of mental illnesses. Furthermore, an earlier study [27] identified emotional life with lower levels of satisfaction as an independent factor for the development of a qi-depressed constitution. This finding is consistent with the current investigation, which revealed an emotional life that was unsatisfactory but unrelated to the incidence of BC. This result confirms that qi-depressed has a different effect on the initiation of BC development than impoverished emotional life.

According to TCM theory, Yang is the basis for the fast growth and metastasis of all malignant cells [27]. Ai Du, the Chinese name for the infectious agent that causes cancer, possesses the quality of "Yang." According to the property, cancer cells can undoubtedly proliferate and cause people to develop Yang-heat constitutions [33]. The current study further demonstrated the validity of our investigation into this issue by showing that, while individual wetness-heat constitution may not be an independent reason for the incidence of BC, it is a superimposed factor of the qi-depressed constitution that encourages the start of BC.

Limitations of the investigation

There were many constraints to the study. The examination of the various TCMC kinds, especially the Qi-depressed constitution, may be biased. Individuals must complete the TCM Physical Constitution Scale based on their clinical manifestations from the previous year, following the diagnostic principles of the scale. However, to assess the effectiveness of TCMCs on the incidence of BC more quantitatively, we asked patients with BC to complete a scale based on their clinical symptoms during the year before the diagnosis. Consequently, when they were hired to promote our study, the majority of the BC patients had received their diagnoses months earlier and had consented to normal treatment. According to earlier research, many patients had severe side effects from normal therapy when they recalled their symptoms from months prior. This could lead to recollection bias eventually [23, 34-40]. Furthermore, the admission criteria were not very challenging or sensible. The purpose of the survey was to investigate how biassed forms of TCMC affected the prevalence of BC. Although the majority of the participants were already in the late stage, this means that patients receive their diagnosis early. Confounding results resulted from the small study population size and the lack of substantial changes in the distribution of distinct TCMC types between stages. Thirdly, the incidence of BC was not significantly impacted by common risk factors for the disease, such as familial BC and reproductive status. For this reason, researchers should use more logical inclusion criteria and a larger sample size in their subsequent research to avoid any bias.

Conclusion

Qi-depressed's constitution is a significant concurrent and contributing factor to the incidence of BC, making it an independent risk factor for BC. The incidence of BC differs amongst different types of biassed TCMC. Although the constitutions of blood stasis and wetness-heat might not be related to the incidence of BC, the combination of the two or the grouping with Qi-depressed might be a risk factor for BC in and of itself. According to this result, TCMC may reveal a new clinical approach for BC inhibition by highlighting the irregularities in people's susceptibilities to progressing BC. This research also provides a reference to observing susceptible constitutions for other severe conditions, such as hypertension and other cancers, which places a lot of emphasis on developing suitable inhibitions and, as a result, greatly promotes the clinical development of TCM.

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Conflict of Interest: None

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