Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

IMPACT OF TRADITIONAL CHINESE MEDICINE CONSTITUTION ON BREAST CANCER INCIDENCE: A CASE-CONTROL AND CROSS-SECTIONAL STUDY

Youzhi Sun[1,2#], Qianjun Chen[3#], Pei Liu[1], Yi Zhao[2], Yanhua He[1], Xiao Zheng[1], Wei Mao[3], Lei Jia[1], Kumar Ganesan[1], Feizhi Mo[1], Jianping Chen[1,3,4*]

1. *School of Chinese Medicine, LKS Faculty of Medicine, University of Hong Kong, Pokfulam, Hong Kong.*
2. *School of Basic Medical Sciences, Jiangxi University of Traditional Chinese Medicine, Nanchang, China.*
3. *The Second People's Hospital of Shenzhen, The First Affiliated Hospital of Shenzhen University, China.*
4. *Hong Kong Breast Cancer Association of Traditional Chinese Medicine, Hong Kong.*

 # These authors contributed equally to the article as first authors.

ARTICLE INFO

Received:
11 Jan 2021
Received in revised form:
18 Apr 2021
Accepted:
20 Apr 2021
Available online:
28 Apr 2021

Keywords: TCMC, Etiology, BC, Pathogenesis, Correlation

ABSTRACT

The term Traditional Chinese Medicine Constitution denotes the unwavering of the body's physical and psychological features. Unbalanced TCMCs generate vulnerability to diseases. This investigation examined the dissemination of the TCMCs of Chinese healthy women and those with breast cancer in Hong Kong to appraise the TCMC efficiency. Healthy woman (n=305) and women with BC (n=305) were recruited for this study to analyze the *Physical Constitution Scale* in TCM, thereby determining the types of TCMC. The sociodemographic data and connected BC risk factors were prepared using questionnaires. The association of unbalanced types of TCMC with BC was determined by multiple factor analysis. The percentage of unbalanced TCMC viz., Qi-depressed, Yin-deficiency, Blood stasis, Qi-deficiency, and Wetness-heat in BC patients was significantly greater than in healthy individuals ($p<0.05$). The analysis of stepwise logistic regression specified the constitution of Qi-depressed was positively correlated with BC (CI 1.49-6.92; OR=3.21). The correlation noteworthy enhanced when the Qi-depressed constitutions shared with Wetness-heat (CI 1.83-12.71; OR=4.82) or Blood-stasis (CI 1.31-8.16; OR=3.27). The grouping of both constitutions was connected to BC (CI 1.02-8.17; OR=2.88). The constitution of qi-depressed was an independent risk factor for BC. Similarly, the constitutions of Wetness-heat and Blood-stasis could also act as major functions in the incidence of BC when grouped with Qi-depressed. This outcome suggests that the unbalanced types of TCMC might be inconsistent in the individual with vulnerabilities to BC, proposing the possibility of Chinese constitutional analysis a potential strategy in detecting the vulnerable populace to BC and the corresponding inhibition of BC.

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To Cite This Article: Sun Y, Chen Q, Liu P, Zhao Y, He Y, Zheng X, et al. Impact of Traditional Chinese Medicine Constitution on Breast Cancer Incidence: A Case-Control and Cross-Sectional Study. Pharmacophore. 2021;12(2):46-56. https://doi.org/10.51847/uqUyzrYobo

Introduction

One of the most common cancers among women is Breast cancer (BC), which is the major cause of malignant demise globally [1-3]. Several innovative diagnoses and treatments of BC have been offered to enhance the rate of survival in patients with BC [4]. However, due to the greater occurrence, Western medicine could not offer a medical "antidote" for BC. About 10-30% of the individuals with BC who experience recurrence and metastasis even though they are undergone standard treatments. Most of the cases may decrease within 5 years [5]. Determining the risk factors and control measures for BC is highly urgent for both physicians and patients with BC. Numerous epidemiological studies and clinical investigations have been executed in the earlier decades, which reported that family history, obesity, physical exercise, alcohol intake, hormonal changes, radiation, and environmental factors are the high-risk factors and contributors to the incidence of BC [6-14]. Some are beyond the limit of the medical practitioners that including family history and aging;

Corresponding Author: Jianping Chen; School of Chinese Medicine, LKS Faculty of Medicine, University of Hong Kong, Pokfulam, Hong Kong. Email: abchen@hku.hk.

others are still debatable and unconvincing factors that are smoking and dietary habit [15-18], and the underlying mechanisms are quite uncertain. Thus, recent medicine still could not enlighten the etiology and effective inhibition of BC.
Since the multifactorial elements of genetics and environmental factors are noteworthily involved in the development of BC, the reasonableness and the inevitability of discovering the etiology and pathogenesis of BC from the fact of TCM Constitution (TCMC) can be merited. In other words, the connection between TCMC and the incidence of BC is a logical alternative for pursuing the etiology and inhibition of BC specified in the systematic approach of TCM.
TCMC denotes the unwavering of the human body's physical and psychological features [19]. The individual constitution is formed based on the inherited stuff and various other factors, including lifestyle and environment [20]. Normally, TCMC is distributed into a balanced (i.e. normality), and an unbalanced (biased), which may be further divided into numerous subclasses, viz., Blood-stasis, Phlegm-wetness, Qi-deficiency, Qi-depressed, Wetness-heat, Yang-deficiency, Yin-deficiency, etc. [21]. A balanced constitution signifies a total health state, while biased constitutions typically reveal an unstable or distressed healthy state, and thereby people are susceptible to get several illnesses. Furthermore, some clinical investigations have substantiated the differences in the constitutional types and occurrence of many diseases. For instance, people with Phlegm-wetness are more prone to get coronary heart disease and hyperlipidemia when compared to other constitutional types [20, 21].
In the last decade, partial clinical data is available related to different types of TCMC and prone to promote the development of BC [22-26]. Regrettably, all studies had various limitations such as sample size, fixed inclusion/exclusion criteria, healthy control, etc. Consequently, no strong clinical decisions were prepared and the connotation between TCMC types and BC was still uncertain. Hence, the current study was made to observe the dissemination of BC across diverse groups of TCMC, examine whether biased TCMC may play as the main risk factor for the development of BC, and create the connection between biased TCMC types and vulnerable factors for BC development.

Materials and Methods

A cross-sectional, retrospective, and case-control study was employed in the present investigation. The recruitment of the 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
i. Local Chinese women
ii. BC was detected using biopsy within a year
iii. Age of more than 20 years
iv. Agreed the informed content
v. Residential in Hong Kong for >3 years prior to the BC diagnosis.

Exclusion Criteria
The exclusion criteria include
i. Individuals with a neurological disorder, psychological disorder
ii. Patients with other classes of malignancy or other physical illnesses.
iii. Those who did not finish the informed consent or questionnaires.

Both criteria for healthy women in the present survey include
i. No analysis of BC, breast, or gynecologic illnesses
ii. No consultation with any doctor for any complaint during 90 days.
iii. Other inclusion/exclusion criteria were indistinguishable from those accepted for employing patients with BC.

Protocol for the Investigation
The ethical endorsement was achieved from the University Research Ethics Board, University of Hong Kong (Ethical number: UW 12-010). Based on the Clinics and workshops, participants were chosen and gave a brief outline of the TCMC study. Participants were asked to fill 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 v.3.1 (EpiData-Association, 2006) and was statistically analyzed into SPSS v.22 (SPSS Inc., Chicago, IL).

Investigation on 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, habit of physical exercise at least one time for every week.
3. TCM Physical Constitution Scale: it was established by Prof. Wang [5] 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 of sixty variable items scored on a five-point scale, that ranged from 1 (not at all) to 5 (very much), and have 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 of the disease characteristics were also included: affected site, clinical-stage, metastasis status, molecular subtype, and time of disease onset.

Data Analysis

Descriptive method was used for the statistical analysis of data. Chi-square test or independent t-test was used for the analysis of each risk factor, TCMC type, patients with variable clinical-stage, 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

About 472 patients with BC participated and 61 refused incomplete questionnaires due to uneducated and thus the response rate was 87 percent. Out of 411, 96 patients were omitted because of non-inhabitant (n=9) in Hong Kong for the last 3years, the diagnosis was performed a year before (n=66), with other illnesses (n=36), with hepatic/renal failure (n=6) or psychological disorders (n=17). Thus, a sum of 305 patients completed their questionnaires, which were presented for the final analyses.

For healthy individual screening, about 1136 participated; 40 were refused for incomplete questionnaires and hence the response rate was 96 percent. Out of 1096, the following patients were omitted based on the criteria: non-inhabitant in Hong Kong (n=23), nutritional or metabolic diseases (n=110), breast diseases or gynecological illnesses (n=312), with other illnesses (n=261), psychological disorders (n=91), and recent visitors to the hospital (n=567). Thus, the sum of 389 healthy individuals was scrutinized, in which 305 women were screened based on their age (45 to 55 years old), educational qualification (upper secondary or higher education), and profession (full-time employment) which were counted for the final analysis. There was no significant difference among those patients with BC and participated healthy individuals **(Figure 1 and Table 1)**.

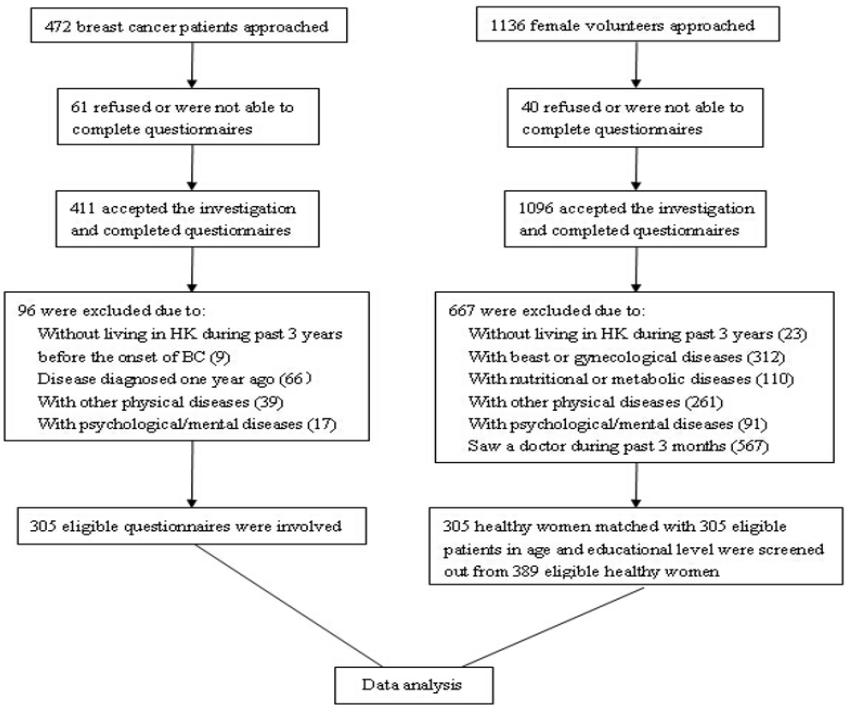


Figure 1. Flow of study participants

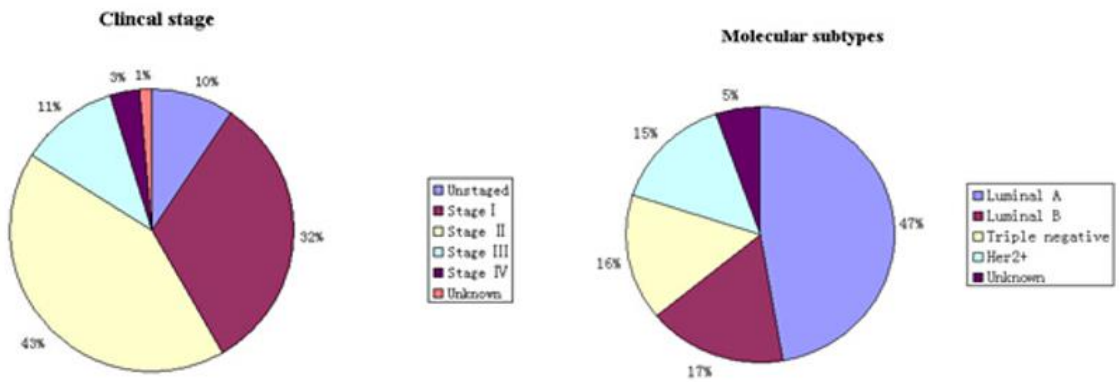
Table 1. The distribution of study based on age, education, occupation, and religion

	Healthy (n = 305)		Patients with BC (n = 305)		P
	N	%	N	%	
Age					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		0.904ᵠ
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	

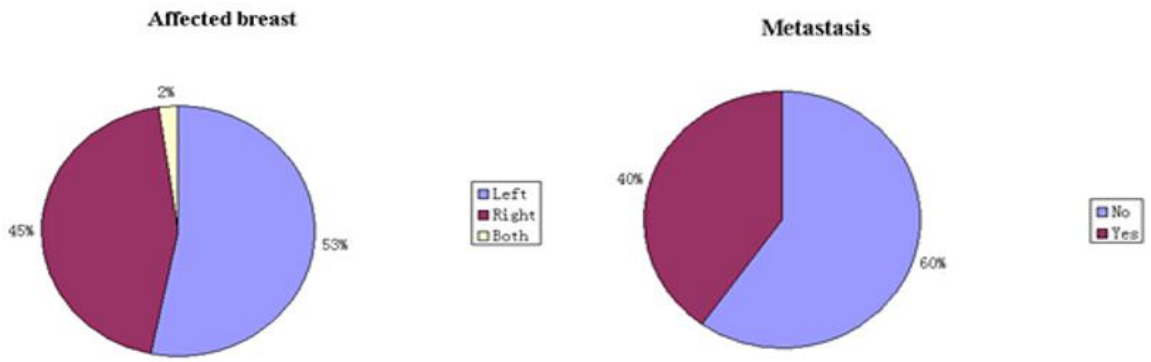
P-value noticeable with ᵠ from student t-test and the others obtained from Chi-square test.

Characteristic Features of the Illness

The characteristics features of the diseases were presented in **Figure 2**. Patients were screened with unilateral cancer (97.7 percent), staged from I to III (83.9 percent), Luminal A (47.2 percent), Luminal B (16.7 percent), Triple-Negative (16.1 percent), and Her2 overexpression (14.8 percent). Cancer metastasis was encountered by above 40 percent of the patient, among them, 38.3 percent were lymph nodes metastasis.



a) b)



c) d)

Figure 2. Disease characteristics of the studied patients with breast cancer

Risk Factors

The common risk factors of BC were presented in **Table 2**. It was a noteworthy difference among patients with BC and healthy individuals in the dissemination of family history and habit of exercise (p<0.001). Contrarily, no significant differences were observed in emotional status, reproductive status, age of menarche, and hormonal use (p>0.5). Furthermore, no significant differences were noticed in other factors such as age, marital status, BMI, smoking, breastfeeding, pregnancy, and alcohol intake (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)	
Breast feeding			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

The distribution of individual TCMC type and their corresponding proportion in patients with BC and healthy women were illustrated in **Figure 3**. The constitutions of Qi- deficiency (38.4%) and Yang-deficiency (31.5%) were the most common type of TCMC among the healthy individual, however, constitutions of Qi-depressed was the intermittent type (19%). Whereas in patients with BC, the constitutions of Qi- deficiency (47.9%) and Qi-depressed (43.9%) were noticed. Furthermore, the occurrence of biased constitutions in patients with BC was noteworthily greater than in healthy individuals. Similarly, the prevalence of Qi-depressed and Yin-deficiency constitutions were also extremely significant ($P<0.01$), and Qi-deficiency and Wetness-heat constitutions were also significant differences ($P<0.05$) among these two groups. The Normality constitution was identified in patients with BC (24.3%) and in a healthy individual (29.2%), however, no significant difference was noticed between them. Also, no noteworthy difference was detected among patients with clinical stages and different molecular subtypes.

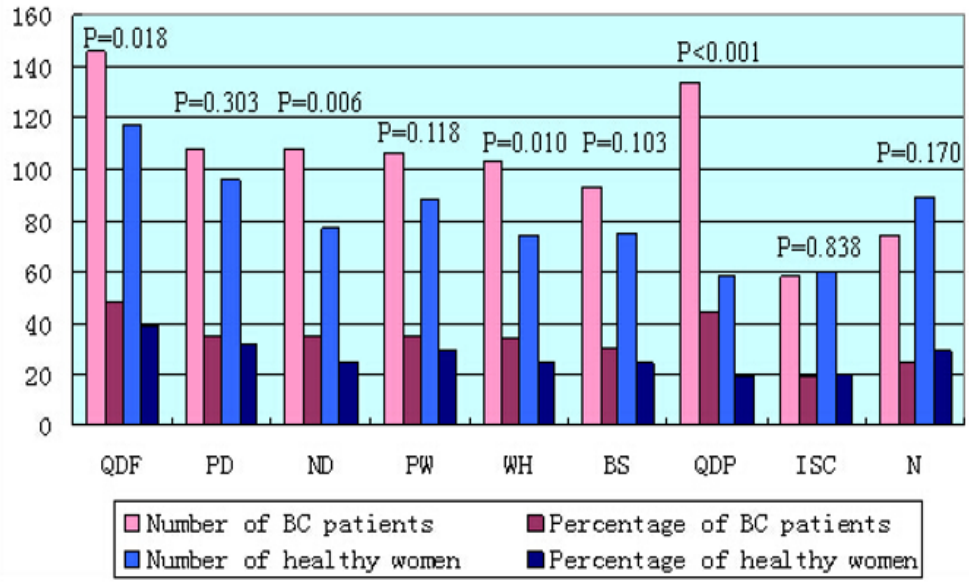


Figure 3. Distribution of TCMC types among the participants (N, %)
Abbreviations: QDF, Qi-deficiency constitution; PD, Yang-deficiency constitution; ND, Yin-deficiency constitution; PW, Phlegm-wetness constitution; WH, Wetness-heat; BS, Blood-stasis constitution; QDP, Qi-depressed constitution; ISC, Inherited Special constitution; N, Normality constitution

TCMC Types and other Factors Connected to the Incidence of BC

The statistical Chi-square test was employed as candidate variables and stepwise logistic analysis, which were used for the identification of susceptible biased TCMC types (Model 1 in **(Table 3)**). The constitution of physical exercise and Qi-depressed was significantly interrelated to BC, representing Qi-depressed could be an independent risk factor. Similarly, identification of two biased TCMC types on the incidence of BC, we used the joined constitutions of two biased as a candidate variable, determining their impacts through 15 stepwise logistic regression models. Based on the outcome, only combined constitutions were considerably related to BC, 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).

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 specifies the person's overall health status and his severe illness conditions. Furthermore, TCMC characterizes its vulnerability and possibilities to find certain illnesses [28]. Hence, TCMC is known to be a potential application in the defense and prevention of diseases through correcting biased TCMC resulting in securing or re-establishing a new balanced TCMC. Balanced TCMC aids to identify and rectify the individual traits, disease onset, and pathologic progression. In recent years, the connection between TCMC and certain diseases are more attracted to TCM professionals and researchers [29]. The current study is also a partial survey insight into TCMC types in patients with BC. Note worthily, this is an opening study utilizing a case-control design, which evaluates the efficacy of biased TCMC on the incidence of BC. This verdict may assist researchers and TCM professionals to better understand the relationship between the incidence of BC and biased TCMC, therefore the outcome of the study may offer a potential reference for those delegates to advance the effective inhibitions and treatment of the diseases.

In the present study, we recognized the biased TCMC types connected to the onset of BC progression. A significant difference was observed in the distribution of biased TCMC types when compared to the healthy individual. The stepwise logistic regression confirmed the common risk factors of BC, and the constitution of Qi-depressed was found to be significant as 3.21(CI 1.49-6.92), representing that the constitution of Qi-depressed can play as a primary independent risk factor for BC. Moreover, the combined constitutions of Qi-depressed and Blood-stasis demonstrate by candidate variables, which are marginally higher value of OR (OR=3.27, CI 1.31-8.16), indicating a fairly significant, however, both combined constitutions contribute to increasing the risk of BC. Similarly, constitutions of Qi-depressed and Wetness-heat show as variables, which are also slightly higher OR of 4.82 (CI 1.83-12.71), proposing the constitutions of Wetness-heat may generate a stronger superposition effect and elevates the menace of BC. Furthermore, the combined constitutions of Wetness-heat and Blood-stasis constitutions could also elevate the menace of BC (CI 1.02-8.17, OR=2.88). The outcomes validate that the constitutions of Blood-stasis, Wetness-heat, and Qi-depressed are strongly connected to the incidence of BC. However, the individual constitutions of Blood-stasis and Wetness-heat did not elevate the menace of BC. On the other hand, the constitution of Qi-depressed could independently elevate the menace of BC. The combined constitutions or with Qi-depressed confirms a remarkable superposition impact and elevates the menace of BC progression.

The constitution of qi-depressed is the main pathological indicator of Liver-qi stagnation, characterized by chest distress, anxiety, depression, doldrums, hypochondriac fullness, irritability, insomnia, and sigh [27]. Based on the TCM theory, Liver-qi stagnation is a causative element for BC development [30]. Our findings are also consistent with the earlier studies that the constitution Qi-depressed is an independent precipitating factor for BC progression, evidencing the rationale behind the attentiveness of TCM on this matter.

It is observed that even though some clinical indices of Qi-depressed constitution are relatively alike to the manifestations of psychological disorders, which are typically linked to unsatisfactory emotional life. The constitution of Qi-depressed in TCM and psychological illnesses in Western medicine is not entirely matching [31]. The key reason is the symptoms of psychological illnesses, which include emotional abnormalities and mood disorders, while the constitution of Qi-depressed is described by both psychological and physiological dysfunctions that includes hypochondriac and chest fullness, and also throat barricade sensation [32]. Thus, Qi-depressed constitution couldn't be measured as the manifestations of psychological diseases. Moreover, an earlier study described emotional life with less satisfaction as an independent factor for the development of Qi-depressed constitution [27], and this result consistent with the present investigation, which showed the unsatisfactory emotional life, and however, it was not connected with the incidence of BC. This outcome validates the effect of Qi-depressed on the onset of BC progression that is un-identical with the influence of deprived emotional life.

All malignant cells have rapidly grown and metastasized, and these features are based on Yang according to the theory of TCM [27]. The infectious agent triggering cancer (called *Ai Du* in Chinese) has the property of 'Yang'. Based on the property, cancer cells can certainly multiply and develop Yang-heat constitutions in the persons [33]. The current study also showed that although individual Wetness-heat constitution may not an independent factor for the incidence of BC, it is a superimposed factor of Qi-depressed constitution that stimulates the BC onset, evidencing the rationality of our study on this matter.

Limitations of the Investigation

The study had numerous boundaries. There may be evoking bias on the analysis of the types of TCMC, particularly on Qi-depressed constitution. Based on the diagnostic principles of TCM Physical Constitution Scale, individuals must complete the scale based on their clinical manifestations during the earlier year. Nevertheless, in this investigation, we inquired patients with BC to complete the scale based on their clinical manifestations during 1 year prior to the diagnosis of BC, which examine the efficacy of TCMCs more quantitatively on the incidence of BC. As an outcome, most of the BC patients were diagnosed several months before and accepted standard therapy when they were employed to communicate our study.

Earlier studies showed that unpleasant complications were raised in many patients due to the standard therapy, when they recalled their manifestations several months earlier, which may cause inevitable recalling bias to a certain point [23, 34-40]. Furthermore, the inclusion criteria were not very difficult and rationale. The survey aimed to explore the effects of biased types of TCMC on the incidence of BC. In this connotation, patients must be diagnosed in the early stage, but many of the participants were already in the late stage. Study population size was small in number and no significant differences were observed in the distribution of individual types of TCMC in various stages, resulting in confound outcomes. Thirdly, common risk factors of BC such as reproductive status and familial BC showed no significant influence on the incidence of BC. Hence, investigators should adopt more rationale inclusion criteria and higher sampling size to avert potential prejudice in their future studies.

Conclusion

The incidence of BC varies in various types of biased TCMC, and the constitution of Qi-depressed is highly concomitant and contributing to the incidence of BC, thus the constitution of Qi-depressed plays as an independent risk factor for BC. The constitutions of Wetness-heat and Blood-stasis may not be involved in the incidence of BC, however, the grouping of both or the grouping with Qi-depressed may be an independent risk factor for BC. This outcome indicates that TCMC could indicate the inconsistency in individuals' and vulnerabilities to BC progression, which may disclose a novel clinical strategy for the inhibition of BC. Furthermore, this investigation offers a reference to sightseeing vulnerable constitutions for other serious illnesses, including hypertension and other cancer types, which gives great attention to evolving appropriate inhibitions, thus, great supports for the clinical and development of TCM.

Acknowledgments: None

Conflict of interest: None

Financial support: This work was sponsored by the National Natural Science Foundation of China (No. 81360513).

Ethics statement: The ethical endorsement was achieved from the University Research Ethics Board, University of Hong Kong (Ethical number: UW 12-010).

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