Modifiable Risk Factors Including Self-Perceived Stress for Breast Cancer in Hong Kong: A Case-Control Study of 10 757 Subject

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Winnie Yeo[1], Lok-Wa Yuen[2], Kelvin Kam-Fai Tsoi[3], Emily Ying-Yang Chan[3], Carol C Kwok[4], Inda Soong[5], Ting-Ying Ng[6], Joanne Chiu[7], Miranda Chan[8], Sharon Wing-Wai Chan[9], Ting-Ting Wong[2], Yolanda Ho-Yan Chan[10], Lawrence Pui-Ki Li[2], Chun-Chung Yau[2], Wai-Ka Hung[2] and Polly Suk-Yee Cheung[2]

[1]Department of Clinical Oncology, Prince of Wales Hospital, Faculty of Medicine, The Chinese University of Hong Kong, Sha Tin, Hong Kong. [2]Department of Surgery, Hong Kong Breast Cancer Foundation, North Point, Hong Kong. [3]Department of Clinical Research and Biostatistics, Jockey Club School of Public Health and Primary Care, Prince of Wales Hospital, Sha Tin, Hong Kong. [4]Department of Clinical Oncology, Princess Margaret Hospital, Kwai Chung, Hong Kong. [5]Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong. [6]Department of Clinical Oncology, Tuen Mun Hospital, Tuen Mun, Hong Kong. [7]Department of Medicine, Queen Mary Hospital, Pok Fu Lam, Hong Kong. [8]Department of Surgery, Kwong Wah Hospital, Yau Ma Tei, Hong Kong. [9]Department of Surgery, United Christian Hospital, Kwun Tong, Hong Kong. [10]Department of Surgery, Breast Health Clinic, CUHK Medical Centre, Sha Tin, Hong Kong.

ABSTRACT

BACKGROUND: In Hong Kong, breast cancer is the commonest female cancer. In addition to intrinsic risk factors that cannot be modified, other factors may be potentially modifiable. The objective of this report was to determine modifiable risk factors in association with breast cancer among Chinese women in our locality.

METHODS: This is a case-control study that enrolled breast cancer patients from the Hong Kong Breast Cancer Registry and healthy matched controls from the local community between 2014 and 2017. Potential risk factors were analyzed using multiple logistic regression.

RESULTS: In total, 5186 breast cancer patients and 5571 controls were recruited. Several modifiable risk factors were identified. Self-perceived high stress level (adjusted odd ratios [AOR] = 3.44; 95% confidence intervals [CI] = 3.13-3.78), dairy-rich diet (AOR = 3.33; 95% CI = 2.01-5.52), delayed child-bearing (AOR = 2.23; 95% CI = 1.79-2.79), meat-rich diet (AOR = 1.77; 95% CI = 1.54-2.04), ever use of oral contraceptives (AOR = 1.34; 95% CI = 1.22-1.47), nulliparity (AOR = 1.21; 95% CI = 1.08-1.35), and being overweight/obese (AOR = 1.21; 95% CI = 1.10-1.32) were found to be associated with an increased risk of breast cancer. On the other hand, breastfeeding (AOR = 0.76; 95% CI = 0.69-0.83) and exercise (odds ratio = 0.62; 95% CI = 0.56-0.68) were associated with decreased risk.

CONCLUSIONS: In our locality, high-stress level, meat- and dairy-rich diet, reproductive history, use of oral contraceptives, and being overweight/obese were identified to be modifiable risk factors for breast cancer. Lifestyle modification may help reduce breast cancer incidence in the coming decades.

KEYWORDS: Modifiable risk factor, stress level, diet, exercise, breast cancer, Chinese

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CORRESPONDING AUTHOR: Winnie Yeo, Department of Clinical Oncology, Prince of Wales Hospital, Faculty of Medicine, The Chinese University of Hong Kong, Sha Tin, Hong Kong. Email: winnieyeo@cuhk.edu.hk

Introduction

Breast cancer is the most common cancer in women worldwide, with the age-standardized incidence being the highest at 112.3 per 100 000 population in Belgium.[1] In Hong Kong, the incidence of breast cancer has been increasing over the past few decades, and breast cancer has become the commonest cancer in Hong Kong women since 1994; this amounted to nearly 5000 newly diagnosed breast cancer patients in 2020 and an age-standardized incidence rate of 66.2 per 100 000 population, which corresponded to over a quarter of all female cancers in Hong Kong.[2] Genetic, reproductive, lifestyle, and mammographic densities are factors associated with the risk of breast cancer development.[3-5] These modifiable and non-modifiable factors contribute to the disparities in the rate of breast cancer between different regions of the world.

Risk factors related to reproductive issues include breastfeeding, which has been consistently shown to have a positive effect against breast cancer, especially in triple-negative

subtype.[4,5] Lactation and number of full-term pregnancies have been reported to be long-term protective factors for luminal subtypes.[6,7] In addition, the use of hormone-based therapies in the capacities of hormonal replacement therapy or oral contraceptives has also been suggested to affect breast cancer risk.[8-10]

Lifestyle factors related to breast cancer development have been increasingly reported. Overweight and obesity, defined by a body mass index (BMI) of 25 and above in Caucasians[11] and 23 and above in Asians,[12] have been studied in association with breast cancer risk.[13] While a positive association exists, especially for postmenopausal hormone-receptor-positive cancers, the contrary has been reported in premenopausal women, where obesity has been associated with lower risk.[4,10,14,15] These contradicting findings highlighted that obesity might affect breast cancer development through age-dependent hormone-related mechanisms. In addition, diet and physical activity have also been associated with breast cancer risk,[16-21] which, in turn, contribute to body weight management.

Another lifestyle factor that has been more recently suggested to be potentially associated with breast cancer risk is stress. Hong Kong has been well-known to be a "stressful" city, with students and workers[22] having reported to be coping with high level of stress daily. According to an international survey, our city has been ranked the fifth most stressful city out of 23 geographical populations.[23]

Studies on risk factors associated with breast cancer have mostly been conducted in Western countries, where the age-standardized incidence rates and demographics differ from the Asian population. The purpose of this study is to investigate both modifiable and non-modifiable risk factors of breast cancer among Chinese women in Hong Kong. We hypothesized that stress was an element in addition to other modifiable and non-modifiable factors associated with breast cancer risk. By identifying modifiable factors, we could potentially empower women with the knowledge that changes in modifiable factors with appropriate interventional strategies could potentially prevent the occurrence of the disease in the local context.

Materials and Methods

Participants

This is a case-control study; breast cancer patients ("cases") and women without cancer ("controls") were recruited from 2014 to 2017. Eligibility for study entry for both cases and controls include women of Chinese ethnicity, aged 18 years or above, who had been living in Hong Kong for at least 5 years prior to study entry. The cases were diagnosed with breast cancer and were registered with the Hong Kong Breast Cancer Registry (HKBCR); they were recruited from major public and private hospitals. The controls were healthy women recruited from different districts in Hong Kong by random sampling from the community including parks, housing estates, city halls, areas outside mass transit railway stations, and other public areas (eg, markets and shopping malls). Recruitments were done between 9:00 and 20:00 hour of the day during the recruitment period. Random sampling was used for selecting subjects in control group; every 10th women passing by the interviewer in the recruitment sites was invited for interview. The study cases and controls were age-matched within 3 years. Breast cancer patients who were diagnosed more than 5 years prior to study entry and cases who had a history of any cancers were excluded from the study.

Standardized questionnaires were administered by trained interviewers. Study factors were selected from questions in the National Cancer Institute—Breast Cancer Risk Assessment Tool (NCI-BCRAT), International Breast Cancer Intervention Study-Breast Cancer Risk Evaluation Tool (IBIS-BCRET), and factors identified in relevant studies in other Asian countries.[2-4]

Ethics approvals were obtained from individual participating centers of the HKBCR. This study was approved by the regional ethics committee of each participating hospitals, namely: The Joint Chinese University of Hong Kong-New Territories East Cluster Institution Review Board of the Chinese University of Hong Kong (CRE2009.037_FR and CRE2010.160), The Chinese University of Hong Kong Survey and Behavioural Research Ethics (SBRE-14-095), Research Ethics Committee of the Kowloon West Cluster (KW/EX/08-090), Research Ethics Committee (Kowloon Central/ Kowloon East) (KC/KE-09-0013/ER-3), Hong Kong East Cluster Research Ethics Committee (HKEC-2011-061), New Territories West Cluster Clinical & Research Ethics Committee (NTWC/CREC/866/10), Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 10-327), Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 09-378), Hong Kong Sanatorium & Hospital Research Committee (RC-2009-02), Hong Kong Baptist Hospital Clinical Research Ethics Committee (with no reference code), and St. Paul's Hospital Ethics Committee (SPH13/EC001). Each of the institutional ethics review board approved the study design, which laid out that verbal consent, instead of written consent, to be obtained from each patient/participant. On this "implied" consent, each patient/participant then proceeded to respond to the questionnaire.

Materials

The current study was conducted using a standardized written questionnaire through face-to-face interviews with all study participants (Appendix 1). The questionnaire collected information on participants' demographics, general health, and modifiable and non-modifiable risk factors. Modifiable factors included smoking history (never, former or current smoker), physical activity (number of hours per week), self-perceived dietary habits (balanced, vegetarian, meat and

dairy-rich diets), self-perceived stress levels (based on a 4-point Likert scale; high-stress level was defined as having over 50% of the participant's time with stress being scored 3 or above out of a Likert scale of 4), BMI; based on the figures provided by the participants,[13] nulliparity and age of first live birth (an ordinal number, with age, arbitrarily categorized as ⩽ or > 35, based on Hong Kong government statistics of average age of pregnancy for local women being 32.9 years[24]), history of breastfeeding, reproductive history (number of live births), and history on the use of oral contraceptives (OCP) and hormone replacement therapy (HRT). Non-modifiable risk factors including family history (only first-degree relatives with breast cancer) was captured; in addition, menstrual history (age at menarche and age at menopause) was captured and included in this category. Pathological data of individual's breast cancer in terms of hormonal receptors statuses [including estrogen receptor (ER) and progesterone receptor (PR)], and human epidermal receptor 2 (HER2) information were extracted from medical records.

Statistical analysis

Odds ratio (OR) of 5 major associating factors including age of first menarche, age of first full-term pregnancy, number of affected first-degree family members, and BMI reported from previous studies in Singapore[25] and Taiwan[26] were used for sample size estimation using the logistic regression procedure of PASS 11. The total sample sizes for 95% confident estimation of the ORs ranged from 8000 to 15 400 (including 10% account for uncertainties). The largest sample size, 5000 women in each arm, was chosen for the study.

All statistical analyses were conducted using the Statistical Package for Social Sciences 22.0. Chi-square test and 1-way analysis of variance were used to compare the distribution of the socio-demographic characteristics and risk factors between the cases and controls. Statistically significant factors ($P < 0.1$) obtained from the univariate analysis were put into multiple logistic regression for further evaluation, where a significance level of 0.05 was adopted. With age controlled, adjusted odds ratio (AOR) and corresponding 95% confidence intervals (CIs) were estimated using hierarchical unconditional multiple logistic regression models with level 1 involving all non-modifiable factors and level 2 incorporating modifiable factors. Hosmer & Lemeshow goodness-of-fit test was used to assess model calibration while receiver operating character curve (ROC; C-statistic) was employed to assess model discrimination. As models with level 1 were not calibrated in both the main analysis and the subgroup analyses, results were presented based on models with level 2 factors.

Results

A total of 10 757 subjects (5186 cases and 5571 controls) completed the whole survey and were included in the current analyses. The controls were recruited between July and September 2014, whereas the cases were recruited over 3 years between 2014 and 2017 subject to the accessibility of patients. The majority (75.3%) of the study participants were aged 40–59. The mean age of the cases and controls were 50.5 and 49.3 years, respectively. The cases and controls were not statistically different in terms of area of residence and education level (Table 1).

The distribution of the potential associated factors for breast cancer among the cases and controls is presented in Table 1. When compared with the controls, there were significantly higher proportions of cases with the following factors: married or cohabitating, positive family history, age at menarche < 12 years, age at menopause > 55 years, being overweight and obese, low physical activity, a diet rich in meat or dairy product, high-stress level, ever smoker, first live birth at age > 35, being nulliparous, absence of breastfeeding, every user of OCP or HRT.

After adjustment for age, multivariate analysis revealed several factors to be associated with the risk of breast cancer (Table 2). Non-modifiable risk factors that were associated with increased risk of breast cancer included a positive family history of breast cancer (AOR = 2.81, 95% CI 2.37-3.34) and early menarche (AOR = 1.40, 95% CI 1.25-1.58). Modifiable factors that were shown to associate with increased risk of breast cancer included overweight and obesity (AOR = 1.19, 95% CI 1.09-1.30), nulliparity (AOR = 1.21, 95% CI 1.08-1.35), first life birth over 35 years (AOR = 2.24, 95% CI 1.80-2.79) and use of OCP (AOR = 1.34, 95% CI 1.22-1.47), meat-rich diet (AOR = 1.77, 95% CI 1.54-2.04), dairy-rich diet (AOR = 3.33, 95% CI 2.01-5.52) and self-perceived high-stress level (AOR = 3.44, 95% CI 3.13-3.78). On the other hand, a history of breastfeeding (AOR = 0.76, 95% CI 0.69-0.83) and physical exercise (AOR = 0.62, 95% CI 0.56-0.68) were associated with a lower risk of breast cancer.

Findings from subgroup analyses based on menopausal status are listed in Table 3. Among postmenopausal participants, the factors identified were similar to those of the overall studied population. Among the premenopausal participants, additional factors that were identified to be associated with a higher risk of breast cancer included being ever smoker, while breastfeeding was not found to be significantly different between the cases and controls. The C-statistics for the models are 0.71 for the overall breast cancer risk model, 0.71 for the premenopausal breast cancer model, and 0.72 for the postmenopausal breast cancer model.

Discussion

This is the first large-scale case-control study to examine factors associated with breast cancer in Hong Kong Chinese women. Many previously reported non-modifiable and modifiable risk factors for breast cancer in the West were also found to be associated with the disease in our local Chinese women. Although non-modifiable factors that were identified included positive familial history and early menarche,[25-27] several modifiable factors were also detected.

Table 1. Demographic characteristics and risk exposures of participants.

	CASES (N=5186)	CONTROLS (N=5571)	*P*
Age, mean (SD), years	50.5 (9.2)	49.3 (9.6)	<.001
Area of residence, No. (%)			
Hong Kong Island	756 (14.6)	823 (14.8)	.937
Kowloon	1136 (21.9)	1227 (22.0)	
New territories	3294 (63.5)	3521 (63.2)	
Marital status, No. (%)			
Married/cohabitating	3919 (75.6)	4431 (79.5)	<.001
Widowed/divorced	487 (9.4)	414 (7.4)	
Never married	780 (15.0)	726 (13.0)	
Education level, No. (%)			
Primary or below	1003 (19.3)	1066 (19.1)	.440
Secondary	2903 (56.0)	3182 (57.1)	
Matriculation or above	1280 (24.7)	1323 (23.7)	
Family breast cancer history, No. (%)	576 (11.1)	220 (3.9)	<.001
Age at menarche, No. (%)			
< Age 12 years	882 (17.0)	649 (11.6)	<.001
⩾ Age 12 years	4304 (83.0)	4922 (88.4)	
Menopausal status, No. (%)			
Premenopausal	3072 (59.2)	3334 (59.8)	.529
Postmenopausal	2114 (40.8)	2237 (40.2)	
Menopause after age 55, No. (%)	242 (7.3)	166 (4.7)	<.001
Body mass index, No. (%)			
Underweight (< 18.5)	397 (7.7)	433 (7.8)	<.001
Normal (18.5-22.9)	2533 (48.8)	3086 (55.4)	
Overweight and obese (⩾ 23)	2256 (43.5)	2052 (36.8)	
Physical activity ⩾ 3 hours/week, No. (%)	1009 (19.5)	1587 (28.5)	<.001
Diet, No. (%)			
Balanced diet	3581 (69.1)	4218 (75.7)	<.001
Rich in vegetarian/vegetable	779 (15.0)	935 (16.8)	
Rich in meat	743 (14.3)	397 (7.1)	
Rich in dairy product	83 (1.6)	21 (0.4)	
Perceived stress > 50% of the time, No. (%)	2137 (41.2)	942 (16.9)	<.001
Current/ex-smoker, No. (%)	285 (5.5)	217 (3.9)	<.001
Reproductive history, No. (%)			

(Continued)

Table 1. (Continued)

	CASES (N=5186)	CONTROLS (N=5571)	*P*
First live birth at age 35 or below	3471 (66.9)	4142 (74.3)	<.001
First live birth at age >35	272 (5.2)	156 (2.8)	
No childbirth	1443 (27.8)	1273 (22.9)	
Ever breastfed, No. (%)	1563 (30.1)	2157 (38.7)	<.001
Ever use of hormonal oral contraceptives, No. (%)	1569 (30.3)	1329 (23.9)	<.001
Ever use of HRT, No. (%)	221 (4.3)	170 (3.1)	.001

Table 2. Risk factors of breast cancer in 10 587 women based on age-controlled multiple logistic regression models.

	AOR (95% CI)	*P*
Age	1.03 (1.02-1.03)	<.001
Family BC history	2.81 (2.37-3.34)	<.001
Early menarche (age < 12)	1.40 (1.25-1.58)	<.001
Body mass index		
Normal (18.5-22.9)	1 (reference)	NA
Underweight (< 18.5)	1.09 (0.93-1.28)	.264
Overweight and obese (≥ 23)	1.19 (1.09-1.30)	<.001
Exercise for ≥ 3 hours per week	0.62 (0.56-0.68)	<.001
Diet		
Balanced diet/rich in vegetable	1 (reference)	NA
Rich in meat	1.77 (1.54-2.04)	<.001
Rich in dairy product	3.33 (2.01-5.52)	<.001
Stress level > 50% of the time	3.44 (3.13-3.78)	<.001
Current/ex-smoker	1.17 (0.96-1.43)	.117
Reproductive history		
First live birth at age 35 or below	1 (reference)	NA
First live birth at age >35	2.24 (1.80-2.79)	<.001
No childbirth	1.21 (1.08-1.35)	.001
Ever breastfed	0.76 (0.69-0.83)	<.001
Ever use of oral contraceptives	1.34 (1.22-1.47)	<.001
Ever use of HRT	1.17 (0.94-1.46)	.157

The present study revealed that a number of well-reported reproductive factors were associated with risk of breast cancer development in our population.[26-30] Women in Hong Kong who were older at the time of their first full-term pregnancy had a higher risk, whereas those who breastfed had a lower risk of breast cancer. On the other hand, our findings were unable to support HRT as a risk factor,[15,28,29] which could be related to the low percentage of cases and controls had ever used HRT (7.7% and 5.2% of HRT-users among postmenopausal cases and controls, respectively). Although meta-analyses have shown conflicting results with regard to the use of OCPs,[28,29,31] the current study identified OCP usage to be a risk factor; unfortunately, the exact components of OCPs consumed were not captured during data collection.

Obesity/overweight was confirmed in our study to be a risk factor. In contrast to most studies where BMI was linked to postmenopausal breast cancer with inconsistent findings among premenopausal women,[5,16,25] our findings revealed BMI to be a significant factor irrespective of menopausal status. Hyperinsulinemia and insulin resistance have been associated with overweight and obesity and contribute to chronic low-grade inflammatory state with secretion of pro-inflammatory cytokines and adipokines,[16,18] creating an environment that promotes carcinogenesis and suppresses apoptosis. It has to be noted that overweight in childhood and early life is likely to be followed by overweight and obesity in adulthood. Thus, maintaining a healthy weight throughout life could be a very important means to protect against breast cancer.[19] The risk of abnormal BMI among postmenopausal could be additionally linked to adipose tissue being their main source of estrogen. Increased weight is associated with higher circulating levels of estrogens, which can contribute to breast carcinogenesis.[18]

The current study also identified high meat and dairy-rich diets to be associated with risk for breast cancer. Diet certainly plays an important role in energy balance and body weight management. Dietary fat, which is rich in red meat, has been associated with higher breast cancer risk,[32,33] whereas consumption of vegetables and fruits has been associated with reduced risk.[34-36] On the other hand, it has been noted that when red meat was substituted with poultry, reduced breast cancer risk has been reported.[37] Although high-heat cooking of red meat results in carcinogenic by-products (eg, polycyclic aromatic hydrocarbons and heterocyclic amines), the often low-temperature cooking means of poultry has not been

Table 3. Subgroup analysis for pre- and postmenopausal women.

	PREMENOPAUSAL				POSTMENOPAUSAL			
	CASES (N = 3072)	CONTROLS (N = 3334)	AOR (95% CI)	*P*	CASES (N = 2114)	CONTROLS (N = 2237)	AOR (95% CI)	*P*
Age, mean years	45.0	43.8	1.04 (1.03-1.05)	<.001	58.5	58.0	1.04 (1.03-1.05)	<.001
Family BC history	313 (10.2%)	116 (3.5%)	2.83 (2.24-3.56)	<.001	263 (12.4%)	104 (4.6%)	2.79 (2.16-3.61)	<.001
Early menarche (age < 12)	578 (18.8%)	421 (12.6%)	1.42 (1.23-1.65)	<.001	304 (14.4%)	228 (10.2%)	1.36 (1.10-1.67)	.004
Body mass index								
Normal (18.5-23)	1617 (52.6%)	2001 (60.0%)	1 (reference)	NA	916 (43.3%)	1085 (48.5%)	1 (reference)	NA
Underweight (< 18.5)	290 (9.4%)	301 (9.0%)	1.19 (0.99-1.44)	.070	107 (5.1%)	132 (5.9%)	0.92 (0.68-1.24)	.585
Overweight and obese (⩾23)	1165 (37.9%)	1032 (31.0%)	1.21 (1.07-1.36)	.002	1091 (51.6%)	1020 (45.6%)	1.17 (1.02-1.34)	.024
Exercise for ⩾3 hours per week	479 (15.6%)	725 (21.7%)	0.70 (0.61-0.81)	<.001	530 (25.1%)	862 (38.5%)	0.56 (0.48-0.65)	<.001
Diet								
Balanced diet/rich in vegetable	2485 (80.9%)	3054 (91.6%)	1 (reference)	NA	1875 (88.7%)	2099 (93.8%)	1 (reference)	NA
Rich in meat	522 (17.0%)	264 (7.9%)	1.96 (1.66-2.33)	<.001	221 (10.5%)	133 (5.9%)	1.46 (1.14-1.87)	.003
Rich in dairy product	65 (2.1%)	16 (0.5%)	3.70 (2.08-6.57)	<.001	18 (0.9%)	5 (0.2%)	2.77 (0.96-7.96)	.059
Stress > 50% of the time	1412 (46.0%)	666 (20.0%)	3.21 (2.86-3.60)	<.001	725 (34.3%)	276 (12.3%)	3.90 (3.29-4.62)	<.001
Current/ex-smoker	223 (7.3%)	162 (4.9%)	1.34 (1.07-1.68)	.012	62 (2.9%)	55 (2.5%)	0.82 (0.55-1.24)	.350
Reproductive history								
First live birth at age 35 or below	1829 (59.5%)	2247 (67.4%)	1 (reference)	NA	1642 (77.7%)	1895 (84.7%)	1 (reference)	NA
First live birth at age > 35	187 (6.1%)	83 (2.5%)	2.71 (2.04-3.61)	<.001	85 (4.0%)	73 (3.3%)	1.58 (1.11-2.26)	.011
No childbirth	1056 (34.4%)	1004 (30.1%)	1.22 (1.07-1.40)	.004	387 (18.3%)	269 (12.0%)	1.46 (1.19-1.78)	<.001
Ever breastfed	932 (30.3%)	1173 (35.2%)	0.91 (0.80-1.04)	.182	631 (29.8%)	984 (44.0%)	0.60 (0.52-0.70)	<.001
Ever use of oral contraceptives	754 (24.5%)	701 (21.0%)	1.17 (1.03-1.33)	.016	815 (38.6%)	628 (28.1%)	1.63 (1.41-1.88)	<.001
Ever use of HRT	58 (1.9%)	54 (1.6%)	1.01 (0.67-1.51)	.971	163 (7.7%)	116 (5.2%)	1.24 (0.95-1.63)	.112

associated with the formation of such by-products.[20] Dairy products such as milk and cheese are rich in fat and can also promote a carcinogenic environment. On the other hand, milk also contains calcium, vitamin D, and conjugated linoleic acids that exert anti-carcinogenic effects by inducing apoptosis, differentiating mammary cells and inhibiting cell cycle progression and angiogenesis.[35,38] However, studies examining the association between low-fat dairy products and breast cancer risk have reported null or negative associations.[39-41] Studies to decipher the role of dairy product consumption in our local population could be difficult as less than 1% of our studied subjects consumed a diary-rich diet.

Our findings also concurred with previous reports that physical activity was a protective factor against breast cancer.[19,34] Physical activity affects a diverse array of metabolic, hormonal, and immunologic pathways. Physical activity reduces body fatness by lowering circulating estrogen levels, insulin resistance, and inflammation, which have been linked to postmenopausal breast cancer development.[42,43] Physical activity can improve innate and acquired immune response and promote tumor surveillance. Physically active individuals also tend to have higher sunlight exposure and, consequently, higher levels of vitamin D, which may modify cell proliferation.[36] As such, potential interventional studies assessing the role of physical activities and inflammation to reduce cancer risk have been suggested.

A relatively unique feature of our study was the inclusion of assessment on self-perceived stress. Psychological stress has been associated with chronic illness and has also been proposed to be one of the contributors to the development of cancers including breast cancer.[44,45] The term "stress" has broad definitions, from stimulus-based or response-based definitions to a dynamic process and beyond. There is no standard method to measure stress to reflect all its aspects.[46] Stress at work,[44] stressful life events,[45] and their subcategories have been assessed, but results have been inconsistent. Although no link was found between breast cancer risk and the occurrence of child death, women suffering the loss of spouse had an average of twofold breast cancer risk.[47,48] These contrasting findings show that psychological stress is a complex issue to quantify in a breast cancer risk model. The precise mechanisms underlying the relationship between psychological stress and cancer remain unclear. Emerging evidence suggests that exposure to stress and stress hormones (eg, cortisol and catecholamines) increase DNA damage.[42] It has also been hypothesized that chronic stress could lead to DNA damage and reduction in the p53 tumor suppressor gene.[43] Moreover, stress could interact with other risk factors, including obesity and smoking, and individual susceptibility to breast cancer.[42,49,50] Stress is subjective and related to personality. The ability to cope with stress and combat stress in life could be a more important factor associated with breast cancer. As such, in the current study, stress was measured subjectively using a Likert scale at a global level to involve all the possible stressors that individual participants faced before the onset of their disease. Our findings showed that women who perceived themselves to have a stressful life had at least a threefold increase in breast cancer risk.

The current study has a few limitations. Most of the information captured was based on the recollection of individual participants. Issues on diet and stress were based on self-perceived responses. The presence of "stress" was recorded based on the subjective impression of an individual. Stress and depression are multifaceted, whereas breast cancer patients may often look for a relationship between the disease and stress, issues with body image, sexual functioning, and social support brought along with the diagnosis of breast cancer may affect patients' perception of the stress experienced prior to cancer diagnosis.[51-53] As such, this factor could have been overestimated. On the other hand, although information on meat intake has been captured, details on the type of meat intake (red meat, white meat, fish, or processed meat, which may differ in cancer risk) have not been included in the questionnaire. Further, the exact type of age of childbirth, duration of breastfeeding, and use of oral contraceptives were not captured in detail. There could also be a chance that our local patient population, like some Asian populations, has taken local herbs as oral contraceptives.[54,55] In addition, body mass index was calculated from figures recalled by the participants and were not measured at the time of study entry; although the duration of sports per week could be quantified, the type and nature of sports activities were not captured. Nonetheless, we attempted to include all information that could be captured in the current analysis. Moreover, this is a case-control study with a representative sample size of nearly 11 000 subjects. Since study patients and healthy controls were recruited from both private and public healthcare centers by random sampling method throughout the territory, the current data is a good representation of the female population in Hong Kong. Additionally, subjective measures, especially with regard to self-perceived stress, are important aspects that have not been included in earlier studies. Moreover, the current report was one of the few that focused on patients of Chinese ethnicity, among whom modifiable risk factors may differ from other geographical regions.

Conclusions

The current study confirmed that most of the well-reported risk factors in association with breast cancer were found in our local Chinese population. Specifically, modifiable risk factors including diet, BMI, and physical activity were identified. Importantly, self-perceived stress was shown to impact breast cancer risk in Hong Kong women. Further confirmation of these findings with investigation into the underlying biological changes induced by stress and its association with breast cancer is warranted. Further, as in the case of ongoing studies among breast cancer survivors, interventional studies in modifying

lifestyle factors, such as providing training for sports to alleviate stress, improve general health and cognitive functioning, and reduce breast cancer risk, are also needed.

Authors' Note

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Author Contributions

Author Contributions: Conceptualization, PSYC; methodology PSYC and WY; data collection, WY, CCK, IS, TYN, JC, MC, SWWC, TTW, LPKL, CCY, WKH, PSYC; formal analysis, LWY, KKFT, EYYC and YHYC; writing—original draft preparation, WY and PSYC; writing—review and editing, WY, LWY, KKFT, EYYC, CCK, IS, TYN, JC, MC, SWWC, TTW, YHYC, LPKL, CCY, WKH, PSYC. All authors have read and agreed to the published version of the manuscript.

Data Availability

All data relevant to the study are included in the article or uploaded as supplementary information. The data are available from the Hong Kong Breast Cancer Foundation, but restrictions apply to the availability of these data. These data were used with permission for the current study, and so are not publicly available. Data are, however, available from the authors (P Cheung and LY Yuen) upon reasonable request. Data will be made available for 15 years from the start of the study.

Ethics Approval and Informed Consents

This study was approved by the regional ethics committee of each participating hospitals, namely: The Joint Chinese University of Hong Kong-New Territories East Cluster Institution Review Board of the Chinese University of Hong Kong (CRE2009.037_FR and CRE2010.160), The Chinese University of Hong Kong Survey and Behavioural Research Ethics (SBRE-14-095), Research Ethics Committee of the Kowloon West Cluster (KW/EX/08-090), Research Ethics Committee (Kowloon Central/ Kowloon East) (KC/KE-09-0013/ER-3), Hong Kong East Cluster Research Ethics Committee (HKEC-2011-061), New Territories West Cluster Clinical & Research Ethics Committee (NTWC/CREC/866/10), Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 10-327), Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 09-378), Hong Kong Sanatorium & Hospital Research Committee (RC-2009-02), Hong Kong Baptist Hospital Clinical Research Ethics Committee (with no reference code), and St. Paul's Hospital Ethics Committee (SPH13/EC001). Each of the institutional ethics review board approved the study design, which laid out that verbal consent, instead of written consent, to be obtained from each patient/participant. On this "implied" consent, each patient/participant then proceeded to respond to the questionnaire.

ORCID iD

Winnie Yeo https://orcid.org/0000-0002-0863-8469

Supplemental Material

Supplemental material for this article is available online.

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