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Impact of WNT1-inducible signaling pathway protein-1 (*WISP-1*) genetic polymorphisms and clinical aspects of breast cancer

Yan Wang, MD[a], Shi-Hui Yang, MD[b], Ping-Wen Hsu, MD[b], Szu-Yu Chien, PhD[b], Chao-Qun Wang, MD[c], Chen-Ming Su, PhD[d,*], Xiao-Fang Dong, MD[a], Yong-Ming Zhao, MD[e], Chih-Hsin Tang, PhD[b,f,g,*]

Abstract

Breast cancer is the most common diagnosed malignancy in women. This study genotyped blood samples from 236 Han Chinese women with breast cancer and 128 healthy controls for single nucleotide polymorphisms (SNPs) rs2977537, rs2929970, rs2929973, rs2977530, and rs62514004, to determine whether these WNT1-inducible signaling pathway protein 1 (*WISP-1*) genetic polymorphisms increase the risk of developing breast cancer. Compared with wild-type (AA) carriers, those carrying the *WISP1* rs62514004 AG or AG + GG genetic variants had a greater risk of developing breast cancer. In an evaluation of the association between clinicopathological aspects and the *WISP1* SNP rs62514004 in the breast cancer cohort, patients with the GG genotype were less likely than those with the AA genotype to develop stage III/IV disease. Patients carrying the *WISP1* rs2929973 GG + TT variant were almost twice as likely as those carrying the GT genotype to have estrogen receptor (ER)- and progesterone receptor (PR)-positive tumors, while those with the *WISP1* rs62514004 AG + GG genetic variants were around twice as likely as those with the AA genotype to have HER2-positive tumors. This study details risk associations between *WISP1* SNPs and breast cancer susceptibility in women of Han Chinese ethnicity.

Abbreviations: AOR = adjusted odds ratio, CI = confidence intervals, ER = estrogen receptor, FSCN1 = fascin-1, HCC = hepatocellular carcinoma, HER2 = human epidermal growth factor receptor type 2, HMGB1 = high-mobility group box protein 1, HWE = Hardy-Weinberg equilibrium, OR = odds ratios, PCR = polymerase chain reaction, PR = progesterone receptor, SNP = single nucleotide polymorphisms, WISP-1 = WNT1-inducible signaling pathway protein-1.

Keywords: breast cancer, single nucleotide polymorphism, WISP-1

1. Introduction

Global cancer estimates for 2018 document breast cancer as the most commonly diagnosed malignancy in women, accounting for around 11.6% of the total cancer incidence burden worldwide.[1] The risk of developing breast cancer is modified by various factors including age, reproductive and gynecological factors, physical activity, consumption of alcohol and tobacco, as well as family history [2] and by gynecological diseases such as adenomyosis and polycystic ovary syndrome.[3,4]

Genetic testing and mammography screening have limited specificity and sensitivity for evaluating an individual's level of risk for breast cancer.[2,5] Instead, single nucleotide polymorphism (SNP) genotyping might better predict an individual's risk for breast cancer and guide disease management.[6,7] Certain SNPs influence the susceptibility to breast cancer.[8] The risk of breast cancer is higher in those carrying *BRCA* gene mutations [9] and the genetic polymorphisms, high-mobility group box protein 1 (*HMGB1*) and fascin-1 (*FSCN1*).[10,11]

WNT1 inducible signaling pathway protein-1 (WISP-1), also known as CCN4, is a cysteine-rich protein that belongs to the CCN superfamily.[12] *WISP-1* is a Wnt-1 and β-catenin responsive gene that contains 5 exons and four introns and maps to human chromosome 8q24.1–8q24.3.[13,14] *WISP-1* is expressed during the processes of embryonic development and tissue repair.[15] Aberrant *WISP-1* expression is seen in various pathological conditions such as arthritis, fibrosis, and malignancy [16] and

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[a] Department of Medical Oncology, Affiliated Dongyang Hospital of Wenzhou Medical University, Dongyang, Zhejiang, China, [b] School of Medicine, China Medical University, Taichung, Taiwan, [c] Department of Pathology, [d] Department of Biomedical Sciences Laboratory, [e] Department of Surgical Oncology, Affiliated Dongyang Hospital of Wenzhou Medical University, Dongyang, Zhejiang, China, [f] Chinese Medicine Research Center, China Medical University, [g] Department of Biotechnology, College of Health Science, Asia University, Taichung, Taiwan.

[*] Correspondence: Chih-Hsin Tang, Department of Pharmacology, School of Medicine, China Medical University, Taichung, Taiwan (e-mail: chtang@mail.cmu.edu.tw); Chen-Ming Su, Department of Biomedical Sciences Laboratory, Affiliated Dongyang Hospital of Wenzhou Medical University, Dongyang, Zhejiang, China (e-mail: proof814@gmail.com).

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promotes the development of various cancers, including chondrosarcoma and oral squamous cell carcinoma.[17–19] *WISP1* genetic polymorphisms are associated with the susceptibility to platinum-based chemotherapy responses as well as platinum-based chemotherapy toxicity in patients with lung cancer.[20,21] *WISP1* SNPs also predict an individual's susceptibility to uterine cervical cancer and hepatocellular carcinoma.[22–24] Up until now, no association has been observed between *WISP1* gene polymorphisms as biomarkers or prognostic factors for breast cancer. This case-control study examined the involvement of five *WISP1* SNPs and clinicopathological features in the susceptibility to breast cancer in a cohort of Han Chinese women.

2. Materials and methods

2.1. Participants

This study enrolled 236 Han Chinese women with breast cancer (cases) presenting to Dongyang People's Hospital (Dongyang, Zhejiang, China) and 128 healthy, community-dwelling women without cancer (controls) between 2014 and 2018; all participants provided one blood sample each at study entry. Tumors were graded by the Scarff-Bloom-Richardson grading system, while the World Health Organization breast tumor classification criteria were used for pathohistological diagnoses.[25] Immunohistochemical evaluations scored all tumors for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor type 2 (HER2) and Ki-67 expression and subtyped them as Luminal A (ER-positive [+] and/or PR^+, HER2-negative [−], Ki-67 <14%), Luminal B (ER^+ and/or PR^+, $HER2^-$, Ki-67 ≥14%, ER^+ and/or PR^+, $HER2^+$), HER2-enriched (ER^-, PR^-, $HER2^+$), or as triple-negative breast cancer (TNBC; ER^-, PR^-, $HER2^-$).[25,26] Clinicopathological information was collected from electronic medical records and from a standardized questionnaire providing sociodemographic data completed by all study participants at study entry. The study protocol was approved by the Dongyang People's Hospital Ethics Committee and all study procedures complied with guidelines and regulations. All study participants provided written informed consent at the time of study entry.

2.2. Genotype determination

Following the manufacturer's instructions, we used QIAamp DNA blood mini kits (Qiagen, Valencia, CA) to isolate total genomic DNA from whole blood specimens. TE buffer (10 mM Tris, 1 mM EDTA, pH 7.8) was used to dissolve DNA, which was stored at −20 °C until quantitative polymerase chain reaction (qPCR) analysis. Five *WISP1* SNPs were selected for analysis (rs2977537, rs2929970, rs2929973, rs2977530, and rs62514004), as they have previously been found to correlate with oral cancer progression.[27] SNPs were genotyped by the TaqMan SNP genotyping assay (Applied Biosystems, Warrington, UK), according to the manufacturer's protocol.[28,29] qPCRs were performed as previously described in a total volume of 20 μL containing Master Mix (10 μL), probes (0.5 μL) and 10 ng of individual genomic DNA. Real-time PCR was performed as previously described, with an initial denaturation step at 95 °C for 10 minutes, then 40 amplification cycles at 95 °C for 15 seconds and 60 °C for 1 minute.[30,31]

2.3. Statistical analysis

Between-group differences were treated as significant when *P* values were less than .05. The SNP genotype distributions were subjected to Chi-square analysis for determining Hardy-Weinberg equilibrium. Demographic comparisons between cases and controls were analyzed using the Mann-Whitney *U* test and the Fisher exact test. Multiple logistic regression models adjusted for confounding variables estimated adjusted odds ratios (AORs) and 95% confidence intervals (CIs) for associations between genotype frequencies and the risk of breast cancer or clinicopathological characteristics. All data were analyzed using the software program Statistical Product and Service Solutions (SPSS) version 19 and are reported as the sample mean ± the standard deviation (SD).

3. Results

All study participants identified as Han Chinese ethnicity (Table 1). Most were nonsmokers (95.31%) and did not drink alcohol (96.09%). The mean age of the controls was significantly

Table 1

Demographical characteristic in 128 controls and 236 patients with breast cancer.

	Control	Patients	*P* value
Variable	**N = 128(%)**	**N = 236(%)**	
Ages (yr)		**Mean ± SD**	**<.001**
	37.98 ± 16.10	53.67 ± 11.58	
Alcohol			**.407**
NO	123 (96.09)	222 (94.06)	
YES	5 (3.91)	14 (5.94)	
Smoke			**.002**
NO	122 (95.31)	236 (100.00)	
YES	6 (4.69)	0 (0.00)	
Tumor size (T)			
≦T2		224 (94.91)	
>T2		12 (5.09)	
Lymph node status (N)			
N0 + N1		186 (78.81)	
N2 + N3		50 (21.19)	
Distant metastasis (M)			
M0		229 (97.03)	
M1		7 (2.97)	
clinical stage			
I/II		183 (77.54)	
III/IV		53 (22.46)	
Histological grade			
G1 + G2		168 (71.19)	
G3 + G4		68 (28.81)	
ER Status			
Negative		73 (30.93)	
Positive		163 (69.07)	
PR Status			
Negative		108 (45.76)	
Positive		128 (54.24)	
HER2 Status			
Negative		148 (62.71)	
Positive		88 (37.29)	

Mann-Whitney, *U* test or Fisher exact text was used between healthy controls and patients with Breast Cancer. * *P* value < .05 as statically significant. T2 = The tumor is larger than 20 mm but not larger than 50 mm; N0 = There's no cancer be found in the lymph nodes or Only areas of cancer smaller than 0.2 mm are in the lymph nodes.; N1 = cancer has spread to 1-3 lymph node (s); N2 = 4-9 lymph nodes; N3 = ≥10 positive lymph nodes; M0 = noninvasive cancer; M1 = cancer has metastasized to organs or lymph nodes away from the breast; G1 = well differentiated (low grade); G2 = moderately differentiated (intermediate grade); G3 = poorly differentiated (high grade); G4 = undifferentiated (high grade). ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PR = progesterone receptor.

Table 2

Odds ratio (OR) and 95% confidence interval (CI) of Breast Cancer associated with *WISP1* genotype frequencies.

Genotype	Control N = 128 (%)	Patients N = 236 (%)	OR (95% CI)	AOR (95% CI)
rs2977537				
AG	59 (46.10)	105 (44.49)	1.00 (reference)	1.00 (reference)
AA	35 (27.34)	78 (33.05)	1.308 (0.857-1.995)	1.186 (0.655-2.149)
GG	34 (26.56)	53 (22.46)	1.002 (0.635-1.581)	0.876 (0.454-1.690)
AA + GG	69 (53.90)	131 (55.51)	1.164 (0.811-1.670)	1.042 (0.620-1.751)
rs2929970				
AG	59 (46.10)	102 (43.22)	1.00 (reference)	1.00 (reference)
AA	40 (31.25)	100 (42.37)	1.358 (0.910-2.026)	1.605 (0.882-2.921)
GG	29 (22.65)	34 (14.41)	0.713 (0.427-1.190)	0.580 (0.285-1.180)
AA + GG	69 (53.90)	134 (56.78)	1.106 (0.770-1.589)	1.147 (0.680-1.935)
rs2929973				
GT	58 (45.31)	101 (42.80)	1.00 (reference)	1.00 (reference)
GG	16 (12.50)	26 (11.01)	1.153 (0.626-2.125)	0.915 (0.391-2.140)
TT	54 (42.19)	109 (46.19)	1.243 (0.849-1.821)	1.320 (0.755-2.306)
GG + TT	70 (54.69)	135 (57.20)	1.225 (0.853-1.760)	1.222 (0.725-2.060)
rs2977530				
AG	57 (44.53)	110 (46.61)	1.00 (reference)	1.00 (reference)
AA	41 (32.03)	74 (31.36)	1.089 (0.719-1.651)	0.911 (0.503-1.651)
GG	30 (23.44)	52 (22.03)	1.131 (0.708-1.806)	0.927 (0.474-1.816)
AA + GG	71 (55.47)	126 (53.39)	1.106 (0.771-1.586)	0.918 (0.546-1.542)
rs62514004				
AA	90 (70.31)	133 (56.36)	1.00 (reference)	1.00 (reference)
AG	20 (15.63)	62 (26.27)	**1.481 (0.954-2.298)***	**2.003 (1.022-3.924)***
GG	18 (14.06)	41 (17.37)	1.655 (0.976-2.806)	1.756 (0.834-3.700)
AG + GG	38 (29.69)	103 (43.64)	**1.545 (1.064-2.245)***	**1.910 (1.101-3.314)***

The odds ratio (OR) with their 95% confidence interval (CI) were estimated by logistic regression models. * P value < .05 as statically significant. The adjusted ORs (AORs) with their 95% CIs were estimated by multiple logistic regression analysis that controlled for tobacco smoking, sex and age.

younger than that of the breast cancer cohort (37.98 years vs 53.67 years; $P < .001$). Most patients (77.54%) had stage I/II breast cancer; 22.46% had stage III/IV disease (Table 1). Most patients (78.81%) had lymph node (N) N1–N3 metastasis. Nearly all tumors (97.03) were classified as non-metastatic (M0) (Table 1). Tumors were classified as ER^+ (69.07%), PR^+ (54.24%), or $HER2^-$ (37.29%). (Table 1)

Table 2 depicts polymorphism frequencies. All genotypes were in Hardy-Weinberg equilibrium ($P > .05$). Of all study participants, most of those with the rs2977537, rs2929970, and rs2977530 SNPs were heterozygous for the AG genotype, most of those with the rs2929973 SNP were heterozygous for the GT genotype, and most of those with the rs62514004 SNP were homozygous for AA (Table 2). In analyses that adjusted for confounders, study participants with the AG or the AG + GG genotype of the *WISP1* rs62514004 polymorphism were around twice as likely to develop breast cancer as compared with those who were AA homozygous (AOR: 2.003; 95% CI: 1.022-3.924 and 1.910; 1.101-3.314, respectively; $P < .05$ for both comparisons). (Table 2)

Conversely, in an evaluation of clinicopathological aspects and rs62514004 *WISP1* genotypes, patients with the GG genotype were less likely than those with the AA genotype to develop stage III/IV disease (OR: 0.315; 95% CI: 0.105-0.949) (Table 3). However, the other genotypes did not have significant difference (data not shown).

ER, PR and HER2 staining can be used to categorize the subtype of breast cancer patients. We found that patients with the *WISP1* rs2929973 GG + TT genotype were almost twice as likely as those with the GT genotype to have tumors with ER and PR positive status (AOR: 1.994; 95% CI: 1.137-3.497 and 1.947; 1.139-3.328, respectively; $P < .05$ for both comparisons), while those carrying the *WISP1* rs62514004 AG + GG genotype were likely as those with the AA genotype to develop HER2 positive status (AOR: 1.881; 95% CI: 1.102-3.211) (Table 4). However, the other genotypes did not have significant difference (data not shown).

4. Discussion

The prognosis of breast cancer patients depends on the clinical or pathological stage at diagnosis. Thus, individuals with hereditary breast cancer could benefit from epigenetic screening for early diagnosis and treatment that prevents the disease from developing. *WISP1* polymorphisms have been identified in various cancers, including uterine cervical cancer and hepatocellular carcinoma,[22–24] but data are scant as to the involvement of *WISP1* polymorphisms in breast cancer. As far as we are aware, our study is the first to investigate the distributions of the rs2977537, rs2929970, rs2929973, rs2977530, and rs62514004 SNPs and their associations with the development and progression of breast cancer in Chinese Han women. Here, we found that women carrying the AG or the AG + GG genotype of the *WISP1* rs62514004 polymorphism were more likely than those with AA homozygotes to develop breast cancer. This evidence implicates critical roles for *WISP1* polymorphisms in breast cancer.

Table 3

Odds ratio (OR) and 95% confidence interval (CI) of a clinical status associated with genotypic frequencies of *WISP1* in 236 Breast Cancer patients.

Genotype	Patients N = 236 (%)		OR (95% CI)	AOR (95% CI)
	Clinical stage			
	I/II	**III/IV**		
rs62514004				
AA	99 (41.95)	34 (14.41)	1.00 (reference)	1.00 (reference)
AG	47 (19.92)	15 (6.36)	0.929 (0.462-1.871)	0.941 (0.466-1.898)
GG	37 (15.68)	4 (1.69)	**0.315 (0.104-0.948)***	**0.315 (0.105-0.949)***
AG + GG	84 (35.59)	19 (8.05)	0.659 (0.350-1.239)	0.661 (0.351-1.245)
	Tumor size (T)			
	≦T2	**>T2**		
rs62514004				
AA	123 (52.12)	10 (4.24)	1.00 (reference)	1.00 (reference)
AG	62 (26.27)	0 (0.00)	0.925 (0.881-0.971)*	
GG	39 (16.53)	2 (0.85)	0.631 (0.133-3.003)	0.629 (0.132-2.997)
AG + GG	101 (42.80)	12 (5.08)	0.244 (0.052-1.137)	0.243 (0.052-1.133)
	Lymph node status (N)			
	N0 + N1	**N2 + N3**		
rs62514004				
AA	101 (42.80)	32 (13.56)	1.00 (reference)	1.00 (reference)
AG	48 (20.34)	14 (5.93)	0.921 (0.450-1.884)	0.931 (0.454-1.909)
GG	37 (15.68)	4 (1.69)	0.341 (0.113-1.031)	0.341 (0.113-1.031)
AG + GG	85 (36.02)	18 (7.63)	0.668 (0.350-1.275)	0.671 (0.352-1.280)
	Distant metastasis (M)			
	M0	**M1**		
rs62514004				
AA	130 (55.08)	3 (1.27)	1.00 (reference)	1.00 (reference)
AG	59 (25.00)	3 (1.27)	2.203 (0.432-11.241)	2.241 (0.432-11.630)
GG	40 (16.95)	1 (0.42)	1.083 (0.110-10.706)	1.070 (0.107-10.684)
AG + GG	99 (41.95)	4 (1.69)	1.751 (0.383-8.002)	1.773 (0.381-8.249)
	Histological grade			
	G1 + G2	**G3 + G4**		
rs62514004				
AA	99 (41.95)	34 (14.41)	1.00 (reference)	1.00 (reference)
AG	41 (17.37)	21 (8.90)	0.491 (0.775-2.870)	1.481 (0.768-2.855)
GG	28 (11.86)	13 (5.51)	1.352 (0.629-2.904)	1.349 (0.626-2.903)
AG + GG	69 (29.24)	34 (14.41)	1.435 (0.815-2.527)	1.428 (0.809-2.518)

The odds ratios (ORs) with their 95% confidence intervals (CIs) were estimated by logistic regression analysis. * P value < .05 as statically significant. The adjusted ORs (AORs) with their 95% CIs were estimated by multiple logistic regression analysis that controlled for tobacco smoking, sex, and age.

Between 2010 and 2014, 5-year relative survival rates for breast cancer were ~90.2% in the USA [32] and ~80% in China.[33] As the prognosis of breast cancer patients depends on their clinical and pathological status at diagnosis, early diagnosis is essential and is becoming ever more possible with improvements in screening strategies and the wider availability of epigenetic strategies.[34] We investigated possible associations between *WISP1* polymorphisms, clinical and pathological markers, and susceptibility to breast cancer. We found that individuals carrying the GG genotype at the rs62514004 *WISP1* polymorphism were more or less to develop stage III/IV disease. In addition, patients with the *WISP1* rs2929973 GG + TT genotype were likely to develop ER and PR positive status. Furthermore, *WISP1* rs62514004 AG + GG genotype were likely as those with the AA genotype to develop HER2 positive status. Our findings contribute to data concerning the correlation between *WISP1* and pathological markers and susceptibility of breast cancer.

The *WISP-1* SNPs has been implicated with cancer progression and susceptibility. *WISP1* SNPs rs16893344, rs2977530, rs2977537 and rs62514004 were significantly associated with susceptibility for lung cancer, while marked correlations were found between the following *WISP1* SNPs and response to platinum-based chemotherapy in the lung cancer cohort.[21] In addition, the *WISP-1* SNPs has been investigated to correlate with the risk of developing hepatocellular carcinoma (HCC). The study authors therefore suggested that *WISP1* SNPs may serve as markers or therapeutic targets for HCC.[24] Furthermore, Lin et al, have suggested the predictive capacity of *WISP1* SNPs for cervical cancer.[22] Our result also supports previous finding that *WISP1* SNPs is plays critical role with cancer development and susceptibility.

Our investigation demonstrates an association between *WISP1* gene variants and susceptibility for breast cancer and its progression among Chinese Han women carrying the *WISP1* rs62514004 polymorphism. WISP-1 appears to be a predictive marker for breast cancer treatment.

Table 4

Odds ratio (OR) and 95% confidence interval (CI) of a clinical status associated with genotypic frequencies of *WISP1* in 236 Breast Cancer patients.

Genotype	Patients N = 236 (%)		OR (95% CI)	AOR (95% CI)
	ER Status			
	Negative	Positive		
rs2929973				
GT	40 (16.95)	61 (25.85)	1.00 (reference)	1.00 (reference)
GG	8 (3.39)	18 (7.63)	1.475 (0.586-3.715)	1.505 (0.593-3.822)
TT	25 (10.59)	84 (35.59)	2.203 (1.211-4.009)*	2.148 (1.177-3.922)
GG + TT	**33 (13.98)**	**102 (43.22)**	**2.207 (1.158-3.547)***	**1.994 (1.137-3.497)***
rs62514004				
AA	38 (16.10)	95 (40.25)	1.00 (reference)	1.00 (reference)
AG	24 (10.17)	38 (16.10)	0.633 (0.336-1.195)	0.638 (0.337-1.208)
GG	11 (4.66)	30 (12.71)	1.091 (0.497-2.396)	1.093 (0.498-2.403)
AG + GG	35 (14.83)	68 (28.81)	0.777 (0.446-1.353)	0.782 (0.448-1.366)
	PR Status			
	Negative	Positive		
rs2929973				
GT	56 (23.73)	45 (19.07)	1.00 (reference)	1.00 (reference)
GG	9 (3.81)	17 (7.20)	2.351 (0.957-5.771)	2.481 (0.989-6.224)
TT	**43 (18.22)**	**66 (27.97)**	**1.910 (1.103-3.308)***	**1.829 (1.040-3.219)***
GG + TT	**52 (22.03)**	**83 (35.17)**	**1.986 (1.177-3.353)***	**1.947 (1.139-3.328)***
rs62514004				
AA	57 (24.15)	76 (32.20)	1.00 (reference)	1.00 (reference)
AG	33 (13.98)	29 (12.29)	0.659 (0.360-1.208)	0.666 (0.359-1.236)
GG	18 (7.63)	23 (9.75)	0.958 (0.473-1.941)	0.967 (0.469-1.991)
AG + GG	51 (21.61)	52 (22.03)	0.765 (0.456-1.282)	0.771 (0.454-1.311)
	HER2 Status			
	Negative	Positive		
rs2929973				
GT	65 (27.54)	36 (15.25)	1.00 (reference)	1.00 (reference)
GG	17 (7.20)	9 (3.81)	0.956 (0.387-2.362)	0.959 (0.388-2.373)
TT	66 (27.97)	43 (18.22)	1.176 (0.672-2.059)	1.189 (0.678-2.086)
GG + TT	83 (35.17)	52 (22.03)	1.131 (0.663-1.931)	1.136 (0.665-1.941)
rs62514004				
AA	92 (38.98)	41 (17.37)	1.00 (reference)	1.00 (reference)
AG	35 (14.83)	27 (11.44)	1.731 (0.929-3.226)	1.730 (0.928-3.224)
GG	21 (8.90)	20 (8.47)	2.137 (1.046-4.366)*	2.135 (1.045-4.363)
AG + GG	**56 (23.73)**	**47 (19.92)**	**1.883 (1.103-3.214)***	**1.881 (1.102-3.211)***

The odds ratios (ORs) with their 95% confidence intervals (CIs) were estimated by logistic regression analysis. * P value $< .05$ as significant. The adjusted ORs (AORs) with their 95% CIs were estimated by multiple logistic regression analysis that controlled for tobacco smoking, sex and age.

Author contributions

Data curation: Yan Wang, Szu-Yu Chien, Chen-Ming Su.
Formal analysis: Szu-Yu Chien.
Investigation: Xiao-Fang Dong, Yong-Ming Zhao.
Methodology: Shi-Hui Yang, Ping-Wen Hsu.
Resources: Yan Wang, Chao-Qun Wang.
Software: Chen-Ming Su.
Supervision: Chen-Ming Su, Chih-Hsin Tang.
Writing – original draft: Chih-Hsin Tang.
Writing – review & editing: Chen-Ming Su, Chih-Hsin Tang.
Chih-Hsin Tang orcid: 0000-0002-7113-8352.

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