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

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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 + 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.\cite{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 \cite{2} and by gynecological diseases such as adenomyosis and polycystic ovary syndrome.\cite{3,4}

Genetic testing and mammography screening have limited specificity and sensitivity for evaluating an individual’s level of risk for breast cancer.\cite{2,3} Instead, single nucleotide polymorphism (SNP) genotyping might better predict an individual’s risk for breast cancer and guide disease management.\cite{5-7} Certain SNPs influence the susceptibility to breast cancer.\cite{8} The risk of breast cancer is higher in those carrying BRCA gene mutations\cite{9} and the genetic polymorphisms, high-mobility group box protein 1 (HMGB1) and fascin-1 (FSCN1).\cite{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.\cite{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.\cite{13,14} WISP-1 is expressed during the processes of embryonic development and tissue repair.\cite{15} Aberrant WISP-1 expression is seen in various pathological conditions such as arthritis, fibrosis, and malignancy\cite{16} and
promotes the development of various cancers, including chondrosarcoma and oral squamous cell carcinoma.\textsuperscript{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.\textsuperscript{20,21} WISP1 SNPs also predict an individual’s susceptibility to uterine cervical cancer and hepatocellular carcinoma.\textsuperscript{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.\textsuperscript{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-).\textsuperscript{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 <67°C for 1 minute, then 40 amplification cycles at 95°C for 15 seconds and 60°C for 1 minute.\textsuperscript{19,31}

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).

### Table 1

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

| Variable                     | Control N=128(%) | Patients N=236(%) | P value |
|------------------------------|------------------|-------------------|---------|
| Ages (yr)                    | 37.96 ± 16.10    | 53.67 ± 11.58     | <.001   |
| Alcohol                      |                  |                   |         |
| NO                           | 123 (96.09)      | 222 (94.06)       |         |
| YES                          | 5 (3.91)         | 14 (5.94)         |         |
| Smoke                        |                  |                   |         |
| NO                           | 122 (95.31)      | 236 (100.00)      |         |
| YES                          | 6 (4.69)         | 0 (0.00)          |         |
| Tumor size (T)               |                  |                   |         |
| ≤T2                          | 224 (94.91)      | 128 (96.09)       |         |
| >T2                          | 12 (5.09)        |                   |         |
| Lymph node status (N)        |                  |                   |         |
| N0 + N1                      | 186 (78.81)      |                   |         |
| N2 + N3                      | 50 (21.19)       |                   |         |
| Distal metastasis (M)        |                  |                   |         |
| MO                           | 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 test was used between healthy controls and patients with Breast Cancer. *P value < .05 as statistically 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; MD = minimvasive 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                | 46 (10.1)           | 44 (44.49)           | 1.00 (reference)         | 1.00 (reference)         |
| AA                | 35 (27.34)          | 33 (33.27)           | 1.00 (reference)         | 1.00 (reference)         |
| GG                | 34 (26.56)          | 23 (22.46)           | 1.00 (reference)         | 1.00 (reference)         |
| AA + GG           | 69 (53.90)          | 53 (55.51)           | 1.164 (0.811-1.670)      | 1.042 (0.620-1.751)      |
| rs2929970         |                     |                      |                          |
| AG                | 46 (10.1)           | 43 (42.23)           | 1.00 (reference)         | 1.00 (reference)         |
| AA                | 40 (32.19)          | 42 (42.37)           | 1.356 (0.910-2.026)      | 1.605 (0.822-2.921)      |
| GG                | 29 (22.65)          | 24 (24.14)           | 0.713 (0.427-1.190)      | 0.589 (0.286-1.190)      |
| AA + GG           | 69 (53.90)          | 65 (65.78)           | 1.106 (0.770-1.589)      | 1.147 (0.680-1.935)      |
| rs2929973         |                     |                      |                          |
| GT                | 45 (36.53)          | 45 (45.49)           | 1.00 (reference)         | 1.00 (reference)         |
| GG                | 41 (33.03)          | 26 (26.36)           | 1.089 (0.719-1.651)      | 0.911 (0.503-1.651)      |
| GG + TT           | 54 (42.19)          | 50 (50.69)           | 1.225 (0.853-1.760)      | 1.222 (0.725-2.060)      |
| rs2977530         |                     |                      |                          |
| AG                | 45 (36.53)          | 41 (41.61)           | 1.00 (reference)         | 1.00 (reference)         |
| AA                | 42 (33.03)          | 31 (31.36)           | 0.713 (0.427-1.190)      | 0.589 (0.286-1.190)      |
| GG                | 30 (23.44)          | 23 (23.14)           | 1.131 (0.708-1.806)      | 0.927 (0.474-1.816)      |
| AA + GG           | 71 (55.47)          | 67 (67.20)           | 1.106 (0.771-1.586)      | 0.918 (0.546-1.542)      |
| rs62514004        |                     |                      |                          |
| AG                | 70 (54.69)          | 70 (70.59)           | 1.106 (0.770-1.589)      | 1.147 (0.680-1.935)      |
| AA + GG           | 69 (53.90)          | 66 (66.78)           | 1.106 (0.770-1.589)      | 1.147 (0.680-1.935)      |
| rs62514004        |                     |                      |                          |
| AG                | 30 (23.44)          | 29 (29.03)           | 1.106 (0.770-1.589)      | 1.147 (0.680-1.935)      |
| AG + GG           | 30 (23.44)          | 29 (29.03)           | 1.106 (0.770-1.589)      | 1.147 (0.680-1.935)      |

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), 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: 1.137-3.211) (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.
Between 2010 and 2014, 5-year relative survival rates for breast cancer were \(\sim 90.2\%\) in the USA \[32\] and \(\sim 80\%\) 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.

### Table 3

| 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) \(\leq T2\) |             |              |              |
| 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) | 0.931 (0.454-1.909) |
|            | 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) \(N0 + N1\) |             |              |              |
| 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 39 (16.53) 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) \(M0\) |             |              |              |
| 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 \(G1 + G2\) |             |              |              |
| 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.
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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 | OR (95% CI) | AOR (95% CI) |
|----------|----------|-------------|--------------|
| rs2929973 |          |             |              |
| ER Status | N = 236 (%) |             |              |
| Negative | 40 (16.95) | 61 (25.85) | 1.00 (reference) | 1.00 (reference) |
| Positive | 8 (3.39)   | 18 (7.63)  | 1.475 (0.586-3.715) | 1.505 (0.593-3.822) |
| 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) |
| GG + TT | 33 (13.98) | 102 (43.22) | 1.077 (0.446-1.353) | 0.782 (0.448-1.366) |
| rs2929973 |          |             |              |
| PR Status | N = 236 (%) |             |              |
| Negative | 9 (3.81)   | 17 (7.20)  | 2.531 (0.957-5.771) | 2.481 (0.989-6.224) |
| Positive | 43 (18.22) | 66 (27.97) | 1.910 (1.103-3.308) | 1.829 (1.040-3.219) |
| rs62514004 |          |             |              |
| AA | 57 (24.15) | 76 (32.20) | 1.091 (0.497-2.396) | 1.093 (0.498-2.403) |
| 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)  | 1.176 (0.672-2.058) | 1.189 (0.678-2.086) |
| AG + GG | 51 (21.61) | 52 (22.03) | 1.091 (0.497-2.396) | 1.093 (0.498-2.403) |
| rs2929973 |          |             |              |
| HER2 Status | N = 236 (%) |             |              |
| Negative | 56 (23.73) | 45 (19.07) | 1.00 (reference) | 1.00 (reference) |
| Positive | 43 (18.22) | 66 (27.97) | 1.910 (1.103-3.308) | 1.829 (1.040-3.219) |
| rs62514004 |          |             |              |
| AA | 92 (38.38) | 41 (17.37) | 1.176 (0.672-2.058) | 1.189 (0.678-2.086) |
| AG | 35 (14.83) | 27 (11.44) | 1.176 (0.672-2.058) | 1.189 (0.678-2.086) |
| GG | 21 (8.90)  | 20 (8.47)  | 1.176 (0.672-2.058) | 1.189 (0.678-2.086) |

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.
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