Lack of Association between rs2067474 Polymorphism in Histamine Receptor H\(_2\) Gene and Breast Cancer in Chinese Han Population

Wen-Ke Cai, Jia-Bin Zhang, Niu-Min Wang, Ying-Lin Wang, Can-Hu Zhao, Jun Lu, and Gong-Hao He

1Department of Cardio-Thoracic Surgery, Kunming General Hospital of Chengdu Military Region, Kunming 650032, China
2Department of Pharmacy, Kunming General Hospital of Chengdu Military Region, Kunming 650032, China
3Hepatobiliary Surgery Center, 302 Hospital, Beijing 100039, China
4Department of Pharmacy, The First Affiliated Hospital of Medical College, Xi\’an Jiaotong University, Xi\’an 710061, China
5Department of Anesthesiology, Affiliated Haikou Hospital, Xiangya School of Medicine, Central South University, Haikou 570208, China

Correspondence should be addressed to Jun Lu; lujun2006@mail.xjtu.edu.cn and Gong-Hao He; gonghow@hotmail.com

Received 6 December 2014; Accepted 13 March 2015

Academic Editor: Jahn M. Nesland

Copyright © 2015 Wen-Ke Cai et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Histamine H\(_2\) receptor (HRH2) was previously suggested to affect the proliferation of breast cancer cells and disease-free survival of breast cancer patients. Furthermore, a common polymorphism, rs2067474, was identified in an enhancer element of the HRH2 gene promoter and was reported to be associated with various diseases including cancer. However, the relationship between this polymorphism and breast cancer risk and malignant degree remains unclear. The aim of this study was to clarify the clinical association of rs2067474 polymorphism with breast cancer. A total of 301 unrelated Chinese Han breast cancer patients and 328 ethnicity-matched health controls were recruited and rs2067474 polymorphism was genotyped. Logistic regression analyses were performed to calculate the odds ratios (ORs) as a measure of association of genotype with breast cancer according to 3 genetic models (dominant, recessive, and additive). Although the percentage of hormone receptor negative cases tended to be higher in AA genotypes, we did not find any significant associations of rs2067474 polymorphism with breast cancer risk or with related clinicopathological parameters in the present study, which indicates that rs2067474 polymorphism of HRH2 gene might not be a risk factor in the development of breast cancer in Chinese Han population.

1. Introduction

Histamine H\(_2\) receptor (HRH2) is a kind of Gs protein-coupled receptor, whose activation stimulates adenyl cyclase and increases intracellular cAMP [1]. This type of histamine receptors was traditionally believed to be mainly expressed in upper gastrointestinal tract, heart, and central nervous system as well and mediated corresponding pathophysiological roles such as gastric muscular atrophy [2], ischemia-induced arrhythmia [3], and schizophrenia [4]. Besides the abovementioned classical places, HRH2 has long been recognized to be expressed in human mammary gland and breast cancer cells [5]. Furthermore, activation of HRH2 in breast cancer cells was reported to increase tumor proliferation [6, 7] and blocking HRH2 was suggested to improve disease-free survival in breast cancer patients [8]. Additionally, HRH2 expressed in other cells (e.g., fibroblasts) was also reported to mediate important effects on the epithelial-to-mesenchymal transition progress of breast cancer cells [9]. These findings strongly indicate that differential expression and function of HRH2 might be a risk factor of breast cancer.

Human HRH2 protein is encoded by HRH2 gene, which is located in chromosome 5q35.2. Within HRH2 gene, one single nucleotide polymorphism (SNP), rs2067474, has gained great attention from investigators today. This SNP results in a G1018A transition located in an enhancer element
of HRH2 gene promoter with a relevant allele frequency in diverse human populations according to previous reports [10] and also HapMap data (http://www.hapmap.org/). It was found that rs2067474 was significantly associated with risk of various diseases including cancer [2, 11–13] and presumed to induce changes in the expression of receptors [14]. Based on the notion that genetic variants (including histamine-related gene polymorphisms) contributed greatly to the development of breast cancer and also to the response to specific treatments and prognosis of the breast cancer patients [15–18], it is rational to hypothesize that rs2067474 might also be associated with breast cancer risk. However, as far as we know, no related investigations have been carried out.

Therefore, the goal of the present study was to demonstrate the relationship between rs2067474 of HRH2 and breast cancer risk by using case-control method among Chinese Han population, hoping to provide further insights into the effect of HRH2 on the development of breast cancer.

2. Materials and Methods

2.1. Subjects. Two hundred and one Chinese Han women with breast cancer were recruited from our previous studies [17, 18], who were admitted to Kunming General Hospital of Chengdu Military Region between 2009 and 2014. Patients who had comorbidity, such as diabetes mellitus, hypertension, or any endocrine disorders, were excluded from the present study. We also recruited 238 unrelated, healthy Chinese Han women from the population of individuals referred for health examination in the same hospital as control group. All the participants in the control group had no known medical illness or hereditary disorders and were not taking any medications. Principal clinical characteristics, such as age at diagnosis, body mass index, and menopausal state, were obtained from the interviewer-administered health risk questionnaires. Menopausal status was defined as the date of last menses followed by 12 months of no menses. The criteria of both the breast cancer patients and health controls according to univariate analysis showed no significant difference in the frequencies of genotypes for patients and 0.107 for controls, respectively. There were 98 patients (48.8%) who were HER-negative (0) or HER-weak positive (1) carriers. Furthermore, 58.0% and 72.1% of the patients were lymph node metastasis carriers and positive for hormone receptors, respectively. There were 98 patients (48.8%) who were HER-negative (0) or HER-weak positive (1) carriers.

2.2. Genotyping Assay. Sample preparation was as previously described [17, 18]. Briefly, the peripheral blood samples were collected into tubes containing ethylenediaminetetraacetic acid and stored at −80°C until analysis. Standard phenol–chloroform extraction method was used to extract genomic DNA from the whole blood. DNA concentration was measured by spectrometry (DU530 UV/VIS spectrophotometer, Beckman Instruments, Fullerton, CA, USA). Polymorphism of rs2067474 was genotyped by amplification-restriction and electrophoresis method as reported previously [14]. The primers used (according to the HRH2 gene sequence Gene Bank Accession number AB023486) were as follows: forward 5’ACA GCC CGT GGC TAA GAA TGG3’ and reverse 5’AGA AGG GAG GCA GGA TGG AAG3’.

2.3. Statistical Analysis. Statistical analyses in the present study were performed with SPSS 18.0 for Windows (PASW Statistics, SPSS Inc., Chicago, IL). The level of significance was set at $P < 0.05$ (two-sided) for all tests. The SNP frequencies in both groups were tested for departure from Hardy–Weinberg Equilibrium (HWE). Student’s $t$-test, analysis of variance (ANOVA), chi-square (Pearson’s $\chi^2$) test or Fisher’s exact test, and unconditional multivariate logistic regression analysis adjusted for age, menopausal state, and body mass index (BMI) were used where necessary according to our previous reports [17, 18]. Odds ratios (ORs) with 95% confidential intervals (CIs) were used to assess the associations between genotypes and breast carcinoma risk or clinical variables.

3. Results

3.1. Participants’ Characteristics. Descriptive clinical characteristics of both the breast cancer patients and health control subjects are listed in Table 1, which shows no significant differences in age and the distribution of menopausal state ($P = 0.381$ and 0.120, resp.) between the cases and controls. However, the BMI values of these two groups exhibit statistical difference ($P = 0.049$). As for breast cancer cases, majority of patients were diagnosed with clinical stage I or II (78.6%) or with ductal invasive carcinoma (87.6%). Furthermore, 58.0% and 72.1% of the patients were lymph node metastasis carriers and positive for hormone receptors, respectively. There were 98 patients (48.8%) who were HER-negative (0) or HER-weak positive (1) carriers.

3.2. Distributions of rs2067474 Genotype and Allele between Breast Cancer Patients and Health Controls. The overall genotype and allele frequencies of rs2067474 in breast cancer cases and health controls are shown in Table 2. The genotype distributions of rs2067474 in both groups were in the expected HWE ($P = 0.152$ for patients and 0.107 for controls, resp.). The minor allele frequency (MAF) of rs2067474 was 0.119 in case group and 0.166 in control group. We found no significant difference in the frequencies of genotypes ($P = 0.174$) or alleles ($P = 0.054$) between breast cancer patients and health controls according to univariate analysis (Table 2). Considering that variables of age, menopausal state, and BMI may affect the development of breast cancer, we


| Table 1: Characteristics of breast cancer patients and control participants. |
|-----------------------------|-----------------------------|-----------------------------|
|                             | Breast cancer (n = 201)     | Control (n = 238)           | P   |
| Age (years)                | 46.5 ± 9.2                  | 47.2 ± 7.9                  | 0.381<sup>a</sup> |
| BMI (kg/m<sup>2</sup>)     | 23.1 ± 2.9                  | 22.6 ± 2.7                  | 0.049<sup>b</sup> |
| Sex                        | Women 201 (100%)            | 238 (100%)                  | —   |
| Menopausal state           | Premenopausal 126 (62.7%)   | 131 (55.0%)                 | 0.120<sup>b</sup> |
| Postmenopausal             | 75 (37.3%)                  | 107 (45.0%)                 |       |
| Tumors size (cm)           | ≤2.0 44 (21.9%)             | 59 (24.8%)                  |       |
|                            | >2.0 157 (78.1%)            | 169 (71.0%)                 |       |
| Histology                  | DIC 176 (87.6%)             | 169 (71.0%)                 | 0.174 |
|                            | LIC 9 (4.4%)                | 59 (24.8%)                  |       |
|                            | Others 16 (8.0%)            | 10 (4.2%)                   |       |
| Clinical stages            | I or II 158 (78.6%)         | 169 (71.0%)                 |       |
|                            | III or IV 43 (21.4%)        | 59 (24.8%)                  |       |
| Lymph node metastasis      | Node-negative 116 (58.0%)   | 131 (55.0%)                 |       |
|                            | Node-positive 85 (42.0%)    | 107 (45.0%)                 |       |
| Hormone receptor status    | Negative 56 (27.9%)         | 59 (24.8%)                  |       |
|                            | Positive 145 (72.1%)        | 107 (45.0%)                 |       |
| HER2 status                | 0-1 98 (48.8%)              | 85 (42.0%)                  |       |
|                            | 2-3 103 (51.2%)             | 145 (72.1%)                 |       |

BMI: body mass index, DIC: ductal invasive carcinoma, and LIC: lobular invasive carcinoma.

<sup>a</sup> <sup>b</sup>P values were calculated by Student’s t-tests.

<sup>b</sup>P values were calculated from two-sided chi-square test.

| Table 2: Frequency distributions of HRH2 rs2067474 genotypes and allele and their associations with the risk of developing breast cancer. |
|-----------------------------|-----------------------------|-----------------------------|
| rs2067474                   | Breast cancer n (%) | Control n (%) | P<sup>a</sup> | OR (95% CI) |
| Genotype                   |                  |                |              |            |
| GG                         | 158 (78.6%)      | 169 (71.0%)    | 0.174        | -          |
| GA                         | 38 (18.9%)       | 59 (24.8%)     |             |            |
| AA                         | 5 (2.5%)         | 10 (4.2%)      |             |            |
| Allele                     |                  |                |              |            |
| G                          | 354 (88.1%)      | 397 (83.4%)    | 0.054        | 0.681      |
| A                          | 48 (11.9%)       | 79 (16.6%)     | (0.463–1.003) |            |

OR: odd ratio, CI: confidence interval, and Ref: reference category.

<sup>a</sup>P values were calculated from two-sided chi-square tests.

Histamine has been known to play many important roles in proliferation, differentiation, and epithelial-to-mesenchymal transition of many kinds of tumors including breast cancer [19–23], whose effects are mediated by 4 different types of histamine receptors (i.e., from H<sub>1</sub> to H<sub>4</sub> receptors), respectively. As a result, the 4 types of histamine receptor genes might all be candidate genes associated with breast cancer. However, recent work has paid much attention to the relationships between breast cancer and two newly discovered histamine receptors (i.e., H<sub>3</sub> and H<sub>4</sub> receptors) [24, 25]. Our previous studies also focused on these two histamine receptors and found that polymorphism of H<sub>4</sub> receptor gene, but not H<sub>3</sub> receptor gene, was associated with the risk and malignant degree of breast cancer in Chinese Han populations [17, 18] while for HRH2 no study focused on the relationship between its gene polymorphism and breast cancer so far. Therefore, elucidating this issue might provide better understandings of how HRH2 affects the development of breast cancer.

Histamine has been known to play many important roles in proliferation, differentiation, and epithelial-to-mesenchymal transition of many kinds of tumors including breast cancer [19–23], whose effects are mediated by 4 different types of histamine receptors (i.e., from H<sub>1</sub> to H<sub>4</sub> receptors), respectively. As a result, the 4 types of histamine receptor genes might all be candidate genes associated with breast cancer. However, recent work has paid much attention to the relationships between breast cancer and two newly discovered histamine receptors (i.e., H<sub>3</sub> and H<sub>4</sub> receptors) [24, 25]. Our previous studies also focused on these two histamine receptors and found that polymorphism of H<sub>4</sub> receptor gene, but not H<sub>3</sub> receptor gene, was associated with the risk and malignant degree of breast cancer in Chinese Han populations [17, 18] while for HRH2 no study focused on the relationship between its gene polymorphism and breast cancer so far. Therefore, elucidating this issue might provide better understandings of how HRH2 affects the development of breast cancer.

Among HRH2 gene polymorphisms, we selected one SNP, rs2067474, in the present study as this SNP was widely studied and reported to be associated with many kinds of diseases [2, 11–14]. Furthermore, this SNP is located in an enhancer element of HRH2 gene promoter and is very likely to affect the transcription and expression of HRH2 [10, 13, 14]. According to the present data, the MAF of rs2067474 in control group (0.166) was close to the allele frequency data of the previous studies on East Asian populations [2] and also HapMap CHB data (http://www.hapmap.org/). Furthermore, the genotype distributions of rs2067474 in both case and control groups were in HWE, which demonstrates that the case-control samples consist of a representative population for the study. However, we did not observe any significant associations between rs2067474 and breast cancer risk in the present study.

It should be mentioned that, although HRH2 was found to be widely expressed in many other cancer cells and was suggested to be related to their proliferation and differentiation [26, 27], early clinical investigations regarding its relationship with breast cancer did not reach a consistent conclusion [28, 29]. This may partially be due to further performed multivariate regression analysis according to 3 different genetic models (i.e., dominant, recessive, and additive genetic models). However, as shown in Table 3, we still did not observe any significant associations (P > 0.05) between rs2067474 polymorphism and breast cancer risk after adjustment for age, menopausal state, and BMI in all of the 3 genetic models.
Table 3: Multivariate analysis for HRH2 rs2067474 polymorphism and risk of breast cancer according to dominant, recessive, and additive genetic models.

|                  | Dominant model | Recessive model | Additive model |
|------------------|----------------|-----------------|---------------|
|                  | \( P^a; \text{OR (95\% CI)} \) | \( P^a; \text{OR (95\% CI)} \) | \( P^a; \text{OR (95\% CI)} \) |
| rs2067474        | 0.065; 0.660 (0.424–1.027) | 0.275; 0.543 (0.182–1.625) | 0.056; 0.696 (0.480–1.010) |

OR: odd ratio; CI: confidence interval.
\( ^a \) \( P \) values were calculated by logistic regression adjusted for age, menopausal state, and body mass index.

Table 4: Correlations of clinicopathological parameters and HRH2 rs2067474 polymorphism in patients with breast cancer.

|                  | GG (\( \text{mean} \pm \text{SD} \)) | rs2067474 | AA (\( \text{mean} \pm \text{SD} \)) | \( P \) |
|------------------|---------------------------------|-----------|---------------------------------|-------|
| Age (years)      | 46.4 ± 9.2                      | 47.1 ± 8.8| 45.6 ± 12.8                     | 0.878\( ^a \) |
| BMI (kg/m\(^2\)) |                                |           |                                 |       |
| \( \geq 25 \)    | 33 (70.2%)                      | 12 (25.5%)| 2 (4.3%)                        | 0.206\( ^b \) |
| \(< 25 \)        | 125 (81.2%)                     | 26 (16.9%)| 3 (1.9%)                        |       |
| Menopausal state |                                |           |                                 |       |
| Premenopausal    | 102 (81.0%)                     | 21 (16.7%)| 3 (2.4%)                        | 0.558\( ^b \) |
| Postmenopausal   | 56 (74.7%)                      | 17 (22.7%)| 2 (2.7%)                        |       |
| Tumor size (cm)  |                                |           |                                 |       |
| \( \leq 2.0 \)   | 37 (84.1%)                      | 5 (11.4%) | 2 (4.5%)                        | 0.203\( ^b \) |
| \( > 2.0 \)      | 121 (77.1%)                     | 33 (21.0%)| 3 (1.9%)                        |       |
| Histology        |                                |           |                                 |       |
| DIC              | 137 (77.8%)                     | 36 (20.5%)| 3 (1.7%)                        | 0.116\( ^b \) |
| LIC              | 8 (88.9%)                       | 1 (11.1%) | 0 (0.0%)                        |       |
| Others           | 13 (81.3%)                      | 1 (6.3%)  | 2 (12.5%)                       |       |
| Clinical stages  |                                |           |                                 |       |
| I or II          | 124 (78.5%)                     | 30 (19.0%)| 4 (2.5%)                        | 1.000\( ^b \) |
| III or IV        | 34 (79.1%)                      | 8 (18.6%) | 1 (2.3%)                        |       |
| Lymph node metastasis |                        |           |                                 |       |
| Node-negative    | 89 (76.7%)                      | 23 (19.8%)| 4 (3.4%)                        | 0.606\( ^b \) |
| Node-positive    | 69 (81.2%)                      | 15 (17.6%)| 1 (1.2%)                        |       |
| Hormone receptor status |                        |           |                                 |       |
| Negative         | 45 (80.4%)                      | 7 (12.5%) | 4 (7.1%)                        | 0.016\( ^b \) |
| Positive         | 113 (77.9%)                     | 31 (21.4%)| 1 (0.7%)                        |       |
| HER2 status      |                                |           |                                 |       |
| 0-1              | 81 (82.7%)                      | 16 (16.3%)| 1 (1.0%)                        | 0.267\( ^b \) |
| 2-3              | 77 (74.8%)                      | 22 (21.4%)| 4 (3.9%)                        |       |
| p53 status       |                                |           |                                 |       |
| Negative         | 41 (78.8%)                      | 9 (17.3%) | 2 (3.8%)                        | 0.31\( ^b \) |
| Positive         | 62 (77.5%)                      | 18 (22.5%)| 0 (0.0%)                        |       |
| Undetermined     | 55 (79.7%)                      | 11 (15.9%)| 3 (4.3%)                        |       |

OR: odd ratio, CI: confidence interval, BMI: body mass index, DIC: ductal invasive carcinoma, LIC: lobular invasive carcinoma, HER2: human epidermal growth factor receptor, and p53: tumor protein 53.
\( ^a \) \( P \) values were calculated by analysis of variance (ANOVA).
\( ^b \) \( P \) values were calculated from two-sided chi-square tests or Fisher’s exact tests.

The interactive hormone promoting effect of the currently available HRH2 antagonists [30–33], which was very likely to mask the eventual HRH2 blocking effect of these HRH2 antagonists. Therefore, since genetic association investigation does not involve the application of any HRH2 antagonists, our present findings may be more persuasive regarding the direct effect of HRH2 on breast cancer compared with previous investigations.

An interesting finding of the present study is that the genotype distribution of rs2067474 was statistically associated with the hormone receptor status. The underlying mechanisms are unknown yet. Some early investigations have
indicated that histamine and HRH2 were involved in the regulation of pituitary hormone secretion [34, 35], which, in turn, might affect the expressions of estrogen receptor or progesterone receptors in breast tissue cells. Future work is needed to elucidate this possibility.

In summary, to our best knowledge, this work is the first study addressing the relationship between HRH2 gene polymorphism and risk of breast cancer. However, no statistical association was observed regarding rs2067474 in this study, which indicates that this HRH2 gene polymorphism might not be a risk factor in the development of breast cancer in Chinese Han population.

Abbreviations
BMI: Body mass index
CI: Confidence interval
DIC: Ductal invasive carcinoma
HRH2: Histamine H2 receptor
HWE: Hardy-Weinberg Equilibrium
LIC: Lobular invasive carcinoma
ORs: Odds ratios.

Conflict of Interests
The authors report no declarations of interests.

Authors’ Contribution
Wen-Ke Cai and Jia-Bin Zhang contributed equally to this work.

Acknowledgments
The authors would like to thank all the volunteers who participated in the present study. This work was supported by grants from the National Natural Science Foundation of China (no. 81460560), the National Science Foundation for Post-Doctoral Scientists of China (no. 2013M532122), the Fundamental Research Funds for the Central Universities (no. 08143047), and the PLA Youth Development Project for Medical Science (no. 13QNP063 and no. 14QNP051).

References
[1] E. Traiffort, M. Ruat, J.-M. Arrang, R. Leurs, D. Piomelli, and J.-C. Schwartz, “Expression of a cloned rat histamine H2 receptor mediating inhibition of arachidonate release and activation of cAMP accumulation,” Proceedings of the National Academy of Sciences of the United States of America, vol. 89, no. 7, pp. 2649–2653, 1992.
[2] H. Yamada, T. Tahara, H. Shiroeda et al., “Effects of -1018G>A polymorphism of HRH2 (rs2607474) on the severity of gastric mucosal atrophy,” Journal of Gastrointestinal and Liver Diseases, vol. 21, no. 2, pp. 139–143, 2012.
[3] G. He, J. Hu, T. Li et al., “Arrhythmogenic effect of sympathetic histamine in mouse hearts subjected to acute ischemia,” Molecular Medicine, vol. 18, no. 1, pp. 1–9, 2012.
[4] H. L. Haas, O. A. Sergeeva, and O. Selbach, “Histamine in the nervous system,” Physiological Reviews, vol. 88, no. 3, pp. I183–1241, 2008.
[5] C. Davio, A. Baldi, A. Mladovan et al., “Expression of histamine receptors in different cell lines derived from mammary gland and human breast carcinomas,” Inflammation Research, vol. 44, no. 1, supplement, pp. S70–S71, 1995.
[6] G. P. Cricco, C. A. Davio, G. Martin et al., “Histamine as an autocrine growth factor in experimental mammary carcinomas,” Agents and Actions, vol. 43, no. 1-2, pp. 17–20, 1994.
[7] C. A. Davio, G. P. Cricco, G. Martin, C. P. Fitzsimons, R. M. Bergoc, and E. S. Rivera, “Effect of histamine on growth and differentiation of the rat mammary gland,” Agents and Actions, vol. 41, pp. CI15–CI17, 1994.
[8] R. Parshad, P. Hazrah, S. Kumar, S. D. Gupta, R. Ray, and S. Bal, “Effect of preoperative short course famotidine on TILs and survival in breast cancer,” Indian Journal of Cancer, vol. 42, no. 4, pp. 185–190, 2005.
[9] J. C. Porrett, N. A. Mohamad, G. A. Martin, and G. P. Cricco, “Fibroblasts induce epithelial to mesenchymal transition in breast tumor cells which is prevented by fibroblasts treatment with histamine in high concentration,” International Journal of Biochemistry and Cell Biology, vol. 51, no. 1, pp. 29–38, 2014.
[10] E. García-Martín, P. Ayuso, C. Martínez, M. Blanca, and J. A. G. Agúndez, “Histamine pharmacogenomics,” Pharmacogenomics, vol. 10, no. 5, pp. 867–883, 2009.
[11] D. Mancama, M. J. Arranz, J. Munro et al., “Investigation of promoter variants of the histamine 1 and 2 receptors in schizophrenia and clozapine response,” Neuroscience Letters, vol. 333, no. 3, pp. 207–211, 2002.
[12] T. Arisawa, T. Tahara, K. Ozaki et al., “Association between common genetic variant of HRH2 and gastric cancer risk,” International Journal of Oncology, vol. 41, no. 2, pp. 497–503, 2012.
[13] T. Nomura, T. Tahara, H. Shiroeda et al., “Influence of HRH2 promoter polymorphism on aberrant DNA methylation of DAPK and CDH1 in the gastric epithelium,” BMC Gastroenterology, vol. 13, no. 1, article 1, 2013.
[14] E. García-Martín, P. Ayuso, A. Luengo, C. Martínez, and J. A. G. Agúndez, “Genetic variability of histamine receptors in patients with Parkinson’s disease,” BMC Medical Genetics, vol. 9, article 15, 2008.
[15] A. González-Neira, “Pharmacogenetics of chemotherapy efficacy in breast cancer,” Pharmacogenomics, vol. 13, no. 6, pp. 677–690, 2012.
[16] C. Justenhoven, O. Obazee, and H. Brauch, “The pharmacogenomics of sex hormone metabolism: breast cancer risk in menopausal hormone therapy,” Pharmacogenomics, vol. 13, no. 6, pp. 659–675, 2012.
[17] G.-H. He, J. Lu, P.-P. Shi et al., “Polymorphisms of human histamine receptor H4 gene are associated with breast cancer in Chinese Han population,” Gene, vol. 519, no. 2, pp. 260–265, 2013.
[18] G.-H. He, J.-J. Lin, W.-K. Cai et al., “Associations of polymorphisms in histidine decarboxylase, histamine-N-methyltransferase and histamine receptor H4 genes with breast cancer,” PLoS ONE, vol. 9, no. 5, Article ID e97728, 2014.
[19] V. Medina, G. Cricco, M. Nuñez et al., “Histamine-mediated signaling processes in human malignant mammary cells,” Cancer Biology and Therapy, vol. 5, no. 11, pp. 1462–1471, 2006.
[20] V. A. Medina and E. S. Rivera, "Histamine receptors and cancer pharmacology," *British Journal of Pharmacology*, vol. 161, no. 4, pp. 755–767, 2010.

[21] B. Blaya, F. Nicolau-Galmés, S. M. Jangi et al., "Histamine and histamine receptor antagonists in cancer biology," *Inflammation and Allergy - Drug Targets*, vol. 9, no. 3, pp. 146–157, 2010.

[22] H. Francis, S. DeMorrow, J. Venter et al., "Inhibition of histidine decarboxylase ablates the autocrine tumorigenic effects of histamine in human cholangiocarcinoma," *Gut*, vol. 61, no. 5, pp. 753–764, 2012.

[23] W.-K. Cai, J. Hu, T. Li et al., "Activation of histamine H4 receptors decreases epithelial-to-mesenchymal transition progress by inhibiting transforming growth factor-β1 signalling pathway in non-small cell lung cancer," *European Journal of Cancer*, vol. 50, no. 6, pp. 1195–1206, 2014.

[24] V. Medina, M. Croci, E. Crescenti et al., "The role of histamine in human mammary carcinogenesis: H3 and H4 receptors as potential therapeutic targets for breast cancer treatment," *Cancer Biology and Therapy*, vol. 7, no. 1, pp. 28–35, 2008.

[25] V. A. Medina, P. G. Brenzoni, D. J. M. Lamas et al., "Role of histamine H4 receptor in breast cancer cell proliferation," *Frontiers in Bioscience*, vol. 3, no. 3, pp. 1042–1060, 2011.

[26] J. Aurelius, A. Martner, M. Brune et al., "Remission maintenance in acute myeloid leukemia: impact of functional histamine H2 receptors expressed by leukemic cells," *Haematologica*, vol. 97, no. 12, pp. 1904–1908, 2012.

[27] R. M. Pagotto, C. Monzón, M. B. Moreno, O. P. Pignataro, and C. Mondillo, "Proliferative effect of histamine on MA-10 Leydig tumor cells mediated through HRH2 activation, transient elevation in cAMP production, and increased extracellular signal-regulated kinase phosphorylation levels," *Biology of Reproduction*, vol. 87, no. 6, article 150, 2012.

[28] P. F. Bowrey, J. King, C. Magarey et al., "Histamine, mast cells and tumour cell proliferation in breast cancer: does preoperative cimetidine administration have an effect?" *British Journal of Cancer*, vol. 82, no. 1, pp. 167–170, 2000.

[29] E. Bolton, J. King, and D. L. Morris, "H2-antagonists in the treatment of colon and breast cancer," *Seminars in Cancer Biology*, vol. 10, no. 1, pp. 3–10, 2000.

[30] J. J. Michnovicz and R. A. Galbraith, "Cimetidine inhibits catechol estrogen metabolism in women," *Metabolism*, vol. 40, no. 2, pp. 170–174, 1991.

[31] S. S. Tworoger, A. H. Eliassen, B. Rosner, P. Sluss, and S. E. Hankinson, "Plasma prolactin concentrations and risk of postmenopausal breast cancer," *Cancer Research*, vol. 64, no. 18, pp. 6814–6819, 2004.

[32] P. F. Coogan, Y. Zhang, J. R. Palmer, B. L. Strom, and L. Rosenberg, "Cimetidine and other histamine2-receptor antagonist use in relation to risk of breast cancer," *Cancer Epidemiology Biomarkers and Prevention*, vol. 14, no. 4, pp. 1012–1015, 2005.

[33] R. W. Mathes, K. E. Malone, J. R. Daling, P. L. Porter, and C. I. Li, "Relationship between histamine2-receptor antagonist medications and risk of invasive breast cancer," *Cancer Epidemiology Biomarkers and Prevention*, vol. 17, no. 1, pp. 67–72, 2008.

[34] J. A. Moguilevsky, B. Szwarcfarb, M. R. Faigon, J. Paolini, and P. Scacchi, "Effects of H1 and H2 histamine receptor antagonists on positive feed-back effect of estrogen on LH in prepubertal female rats," *Hormone and Metabolic Research*, vol. 21, no. 12, pp. 658–660, 1989.

[35] U. Knigge and J. Warberg, "The role of histamine in the neuroendocrine regulation of pituitary hormone secretion," *Acta Endocrinologica*, vol. 124, no. 6, pp. 609–619, 1991.