Pathology - Research and Practice 215 (2019) 152518

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

# Association of CAV1 polymorphisms with the risks of breast cancer: A systematic review and meta-analysis

Cunye Yan[a,1], Chenyu Sun[e,1], Xiuxiu Ding[b], Feras Kamel Rizeq[c], Min Ren[a], Fan Yang[d], Ying Chen[a], Benzhong Wang[a,*]

[a] Department of Breast Surgery, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, 218 JiXi Avenue, Hefei, 230022, Anhui, PR China
[b] Lianhua Community Health Service Centre, The Second Affiliated Hospital of Anhui Medical University, 217 Furong Street, Hefei, Anhui, PR China
[c] Avalon University School of Medicine, Santa Rosaweg 122-124, Willemstad, Curaçao
[d] Maternal and Chile Health Care Hospital of Anhui Province, No.15 Yimin Street, Hefei, 230001, Anhui, PR China
[e] AMITA Health Saint Joseph Hospital Chicago, 2900 N. Lake Shore Drive, Chicago, IL 60657, USA

ARTICLE INFO

*Keywords:*
Caveolin-1
CAV1 polymorphism
Breast cancer
Meta-analysis

ABSTRACT

*Background:* Caveolin-1 (CAV1) polymorphisms have been shown to correlated with breast cancer risk in previous studies. However, the role of CAV1 polymorphisms still remained indecisive, and dual functions of CAV1 was demonstrated in breast cancer development. Consequently, a meta-analysis to evaluate and summarize the association of the CAV1 polymorphisms with breast cancer susceptibility.

*Material and methods:* Extensive search was performed in PubMed, Web of Science, Google scholar, EMBASE.com, CNKI and Wanfang searching platform up to March 2019. The Newcastle–Ottawa Scale (NOS) were used to evaluate the quality of each study. The Odds ratios (ORs) and the 95% confidence intervals (CIs) were analyzed to evaluate the strength of the associations in five genetic models. Inter-study heterogeneity was quantified using the I-squared ($I^2$) test. In addition, the Egger's test and Begg's test were applied to evaluate the publication bias.

*Results:* 4 case-control studies with 2115 cases and 2138 controls were enrolled into this analysis. There was a significant association between rs3807987 polymorphism of CAV1 and breast cancer in allele comparison (A vs. G: OR = 1.288, 95%CI = 1.162–1.428, $P < 0.001$), heterozygote comparison (AG vs. GG: OR= 1.422, 95%CI=1.233–1.639, $P < 0.001$), and dominant comparison (AA+AG vs. GG: OR=1.395, 95%CI=1.228-1.586, $P < 0.001$). A significant association of rs3807987 polymorphism in allele comparison (A vs. G: OR=1.238, 95%CI=1.109–1.383, $P < 0.001$), heterozygote comparison (AG VS. GG: OR=1.466, 95%CI=1.267–1.697, $P < 0.05$), and dominant comparison (AA+AG vs. GG: OR=1.384, 95%CI=1.209–1.585, $P < 0.001$) was also founded amongst Chinese population. A significant association between rs7804372 polymorphism and breast cancer amongst Chinese population in recessive comparison (AA vs. AT + TT: OR = 0.730, 95%CI = 0.567–0.940, $P = 0.015$) was identified. No significant association between breast cancer risk and rs1997623 was found.

*Conclusion:* CAV1 rs3807987 and rs7804372 polymorphisms are associated with the change of breast cancer risk. More well-designed and large studies in various populations are needed to further elaborate these associations.

## 1. Introduction

Breast cancer (BC) as of today is the most frequent cause of cancer and the leading cause of death in women across the world [1,2]. In 2018, approximately 266,000 new cases of breast cancer, with 41,000 cases of deaths, were estimated to occur in women in the United States [3]. It has been confirmed that breast cancer is more common amongst women whose first-degree relatives are diagnosed of the disease, compared with the general population [4]. Among all BC cases, approximately 5–10% are due to an inherited predisposition, caused by mutations in susceptibility genes [5]. Caveolin-1 (CAV1), one of the genes that is involved in the breast cancer growth [6], has drawn the

* Corresponding author.
*E-mail address:* benzhongwang@163.com (B. Wang).
[1] Cunye Yan and Chenyu Sun contributed equally to this work.

https://doi.org/10.1016/j.prp.2019.152518
Received 11 March 2019; Received in revised form 1 June 2019; Accepted 26 June 2019

attention of clinicians and researchers.

CAV1 gene is located on the human chromosome 7 (7q31.1) and contains 3 exons. It encodes the protein caveolin-1 mainly in epithelial and endothelial cells, fibroblasts and adipocyte. Caveolin-1 is an essential structural component of caveolae [6–8]. Caveolae is a tiny vesicular invagination that is part of the cell membrane. It is within this organelle that cells perform various cellular processes such as potocytosis, transcytosis and signal transduction. This is important because through a myriad of cell signaling and transport ways, caveolae protein could regulate cellular processes, and the domains that are enriched of cholesterol and sphingolipids could initiate caveolae-mediated endocytosis [9].

Aforementioned studies suggested that CAV1 may either promote tumor growth or play a role of a tumor suppressor, depending on polymorphisms of CAV1 and tumor types [10]. Its dual roles depend on the polymorphism of CAV1 and different types of tumors [11]. It has been reported that some CAV1 mutations were associated with breast cancer risk [12]. Caveolin-1 has been shown to suppress breast cancer by acting as a stimulating factor for BRCA1 protein and MRNA levels, but interestingly, less expression of caveolin-1 in normal tissues in comparison to BC tissue was also reported [13,14]. Several publications have investigated the influence of CAV1 polymorphisms in breast cancer, but their results remained controversial [15,16]. Therefore, we performed meta-analyses to evaluate and summarize the contribution of the CAV1 polymorphisms to breast cancer susceptibility.

## 2. Materials and methods

### 2.1. Publication search

We conducted and monitored numerous databases to retrieve valuable and relevant data in regards to our analysis. Examples such as PubMed, Web of Science, EMBASE.com, CNKI and Wanfang searching platform were all carefully examined from us in order to complete and have a valid meta-analysis. The search terms were as follows: ((Caveolin-1) OR (CAV1) OR (Cell Growth-Inhibiting Protein 32)) AND (breast) AND (cancer OR carcinoma OR tumor OR neoplasms) AND (polymorphism OR SNP OR mutation OR genotype OR variant). The latest updated date of literature retrieval was March 2019. We also manually reviewed the references of retrieved articles or textbooks for additional eligible studies. Irrelevant articles were excluded by evaluating the titles and abstracts. We then read the full text of the remaining articles that potentially met our inclusion criteria to include eligible studies. This report was directed and rendered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement on reporting meta-analysis [17].

### 2.2. Inclusion criteria

1) The study was a case-control or cohort study in regards to the association between CAV1 and breast cancer risk. 2) The study had enough research data to calculate odds ratios (ORs) and their 95% confidence intervals (95%CIs). 3) Only single nucleotide polymorphisms (SNPs) with three or more studies on one polymorphism were included in our analysis.

### 2.3. Exclusion criteria

1) Not case-control or cohort studies. 2) Studies on animal models or cell lines. 3) Studies not relevant to breast cancer. 4) Lack or incompleteness of genotyping data. 5) Repetitive publications.

### 2.4. Data extraction

Two researchers (Cunye Yan & Chenyu Sun) independently analyzed and extracted data, according to the aforementioned inclusion and exclusion criteria. The following information was extracted: publication year, first author's name, cancer type, ethnicity, genotyping method, source of control groups, and the genotype frequencies in cases and controls. Mutual consensus was reached through discussion.

### 2.5. Study quality assessment

To ensure the quality of the studies included in this analysis, the Newcastle–Ottawa Scale (NOS) to evaluate the quality of each study was used: study ratings of seven to nine stars indicated a high quality, five to six stars indicated a moderate quality, and four stars or fewer indicated a low quality [18,19]. Two reviewers completed assessments independently, and any disagreements were resolved by discussion.

### 2.6. Statistical analysis

STATA 12.0 software (STATA Corp, College Station, TX) was used for statistical analysis. The relationship between CAV1 polymorphism and susceptibility to breast cancer was assessed with ORs and 95% CIs. Heterogeneity among the studies was assessed by the $I^2$ statistics [20]. The heterogeneity was considered significant when $I^2 > 50\%$ [21]. When $I^2 \leq 25\%$, variation between studies was only caused by sampling errors, meaning a small heterogeneity; when $I^2$ was between 25% and 50%, moderate heterogeneity was considered; when $I^2 > 50\%$, high heterogeneity was considered [22,23]. We used the fixed effects model to calculate the pooled OR estimate if heterogeneity was not significant, and otherwise, we used the random-effects model [24,25]. Each site was divided into five models: allelic comparison, homozygote comparison, heterozygote comparison, dominant model, and recessive model. For example, the CAV1 rs3807987 polymorphism was divided into allelic comparison (A VS. G), homozygote comparison (AA VS. GG), heterozygote comparison (AG VS. GG), dominant model (AA + AG VS.GG) and recessive model (AA VS.AG + GG). For the sake of explore the differences caused by the national factors included in the study, we conducted a more in-depth sub-group analysis of the data from countries. In order to assess the stability of inclusion studies, we conducted a sensitivity analysis of all studies. Publication bias was assessed qualitatively by visually inspecting symmetry of funnel plots, and quantitatively by Begg's test and Egger's test to further quantitatively analysis. All statistical results were considered to have statistical significance when $P < 0.05$.

## 3. Results

### 3.1. Literature search

A total of 382 studies potentially relevant articles were initially identified after searching several databases according to search strategy. Through scanning the title and abstract, 358 studies articles were excluded, including overlapping articles, review articles, and uncorrelated articles. Full texts of the 24 studies remaining articles were scrutinized. 13 articles were excluded because they were not case-control studies or cohort studies. 7 articles were excluded because they did not have enough data to extract. Finally, 4 studies meeting the included criteria were included [15,16,26,27]. The Publication search flow diagram is shown in Fig. 1.

### 3.2. Study characteristics

A total of 2115 cases and 2138 controls were included in this analysis. Two studies were conducted among Chinese publications [15,16] and two among Iranian populations [26,27]. Based on the Newcastle-Ottawa (NOS) Scale, the 4 included studies were all high quality studies, with NOS scores ranging from seven stars to eight stars (Table S1). Detailed information of all studies in this analysis is shown in the Table 1.

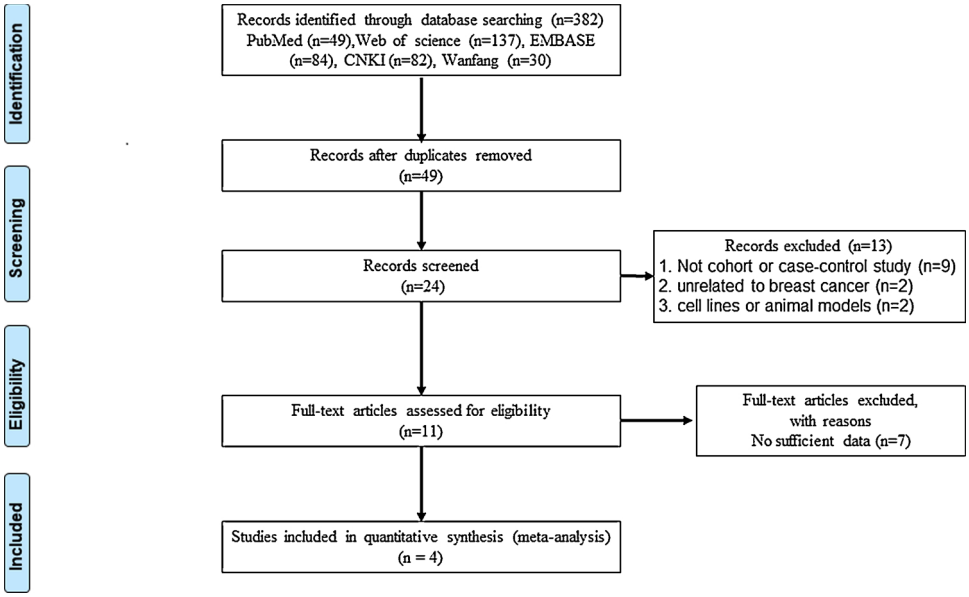


**Fig. 1.** Flow chart presenting the study selection procedure.

### 3.3. Quantitative analysis

The association between CAV1 gene polymorphism and the risk of breast cancer disease is shown in the Table 2. According to the results, we found a significant association between rs3807987 polymorphism of CAV1 and breast cancer in allele comparison (A vs. G: OR = 1.288, 95%CI = 1.162–1.428, $P < 0.001$) (Fig. 2), heterozygote comparison (AG vs. GG: OR = 1.422, 95%CI = 1.233–1.639, $P < 0.001$) (Fig. 3), and dominant comparison (AA + AG vs. GG: OR = 1.395, 95%CI = 1.228–1.586, $P < 0.001$) (Fig. 4). In the subsequent subgroup analysis of Chinese population, we found a significant association in allele comparison (A vs. G: OR = 1.238, 95%CI = 1.109–1.383, $P < 0.001$) (Fig. 2), heterozygote comparison (AG VS. GG: OR = 1.466, 95%CI = 1.267–1.697, $P < 0.05$) (Fig. 3), and dominant comparison (AA + AG vs. GG: OR = 1.384, 95%CI = 1.209–1.585, $P < 0.001$) (Fig. 4). In the analysis of rs7804372, we also found a significant association between rs7804372 polymorphism and breast cancer among Chinese population in recessive comparison (AA vs. AT + TT: OR = 0.730, 95%CI = 0.567-0.940, $P = 0.015$, Fig. 5). No significant associations between breast cancer risk and rs1997623 was found.

### 3.4. Sensitivity analyses and publication bias

We conducted sensitivity analysis of each SNP by changing the random model to fix model or visa versa. The results are shown in Table 3. No obvious publication bias was detected by quantitative analyses of Begg's test and Egger's test (Table 4).

## 4. Discussion

Tumor activating genes and tumor suppressor genes play an essential role in the development of cancer [28]. CAV1 is an integral membrane protein abundantly expressed in endothelial cells (EC), adipocytes, fibroblasts, and muscle cells [29–31]. CAV1 was reported to be mutated or overexpressed in a number of different solid tumors, and played an important role in carcinogenesis [32–36]. The exact roles of CAV1 in cancer development might be completely different in different types of cancer [11]. For example, an overexpression of CAV1 in lung squamous cell carcinoma (SCC) might be associated with tumor extension, metastasis and poor prognosis, while the down-regulation and loss of CAV1 might be associated with tumor progression in lung adenocarcinoma [37–40]. In terms of breast cancer, some CAV1 mutations were shown to be associated with an increased risk [12]. The loss of CAV1 could lead to the proliferation, progression, and angiogenesis of tumors [41]. Due to the complicated roles of its function in

**Table 1**
Main Characteristics of CAV1 Studies.

| SNP | First Author | Year | Ethnicity | Genotyping Method | Source of control | NOS Score | HWE | Case | | | Controls | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | AA | AB | BB | AA | AB | BB |
| rs380798 | Fard et al. | 2018 | Iranian | PCR | HB | 8 | N | 105 | 22 | 76 | 125 | 31 | 47 |
| | Wang et al. | 2017 | Chinese | MassARRAY | HB | 8 | Y | 345 | 193 | 22 | 400 | 159 | 24 |
| | Liu et al. | 2011 | Chinese | PCR | HB | 7 | N | 704 | 409 | 119 | 801 | 311 | 120 |
| rs1997623 | Fard et al. | 2018 | Iranian | PCR | HB | 7 | N | 94 | 43 | 66 | 122 | 22 | 59 |
| | Wang et al. | 2017 | Chinese | MassARRAY | HB | 8 | Y | 507 | 51 | 2 | 509 | 70 | 4 |
| | Liu et al. | 2011 | Chinese | PCR | HB | 7 | N | 1179 | 52 | 2 | 1190 | 39 | 3 |
| rs7804372 | Fard et al. | 2018 | Iranian | PCR | HB | 8 | Y | 96 | 65 | 42 | 106 | 74 | 23 |
| | Wang et al. | 2017 | Chinese | MassARRAY | HB | 8 | Y | 317 | 207 | 36 | 338 | 202 | 42 |
| | Hamta et al. | 2016 | Iranian | PCR | HB | 7 | Y | 84 | 29 | 7 | 59 | 49 | 12 |
| | Liu et al. | 2011 | Chinese | PCR | HB | 7 | Y | 745 | 410 | 77 | 649 | 472 | 111 |

NOS: Newcastle-Ottawa Scale; H-B: hospital-based; P-B: population-based ; AA: homozygotes for the wildtype allele; AB: hetero-Zygotes; BB: homozygous for the mutant allele.

**Table 2**
Results of meta-analysis for polymorphisms in CAV1 and breast cancer susceptibility.

| SNP | Comparison | Subgroup | N | PH | PZ | Effects model | OR (95% CI) | $I^2$ |
|---|---|---|---|---|---|---|---|---|
| rs3807987 | A VS. G | Overall | 3 | 0.146 | 0.000 | Fixed | 1.288(1.162-1.428) | 48.0% |
| | AA VS. GG | | 3 | 0.111 | 0.029 | Random | 1.318(0.918-1.892) | 54.5% |
| | AG VS. GG | | 3 | 0.206 | 0.000 | Fixed | 1.422(1.233-1.639) | 36.8% |
| | AA + AG VS.GG | | 3 | 0.925 | 0.000 | Fixed | 1.395(1.228-1.586) | 0.0% |
| | AA VS.AG + GG | | 3 | 0.021 | 0.382 | Random | 1.235(0.770-1.981) | 74.0% |
| | A VS. G | Chinese | 2 | 0.963 | 0.000 | Fixed | 1.238(1.109-1.383) | 0.0% |
| | AA VS. GG | | 2 | 0.858 | 0.384 | Fixed | 1.117(0.871-1.431) | 0.0% |
| | AG VS. GG | | 2 | 0.699 | 0.000 | Fixed | 1.466(1.267-1.697) | 0.0% |
| | AA + AG VS.GG | | 2 | 0.878 | 0.000 | Fixed | 1.384(1.209-1.585) | 0.0% |
| | AA VS.AG + GG | | 2 | 0.905 | 0.898 | Fixed | 0.984(0.772-1.255) | 0.0% |
| rs1997623 | A VS. C | Overall | 3 | 0.010 | 0.671 | Random | 1.097(0.717-1.677) | 78.3% |
| | AA VS. CC | | 3 | 0.375 | 0.216 | Fixed | 1.298(0.859-1.960) | 0.0% |
| | AC VS. CC | | 3 | 0.001 | 0.419 | Random | 1.319(0.674-2.578) | 84.7% |
| | AA + AC VS.CC | | 3 | 0.005 | 0.552 | Random | 1.172(0.694-1.982) | 81.4% |
| | AA VS.AC + CC | | 3 | 0.564 | 0.677 | Fixed | 1.088(0.732-1.618) | 0.0% |
| | A VS. C | Chinese | 2 | 0.043 | 0.827 | Random | 0.942(0.549-1.615) | 75.7% |
| | AA VS. CC | | 2 | 0.816 | 0.379 | Fixed | 0.575(0.168-1.970) | 0.0% |
| | AC VS. CC | | 2 | 0.036 | 0.961 | Random | 0.985(0.542-1.790) | 77.3% |
| | AA + AC VS.CC | | 2 | 0.037 | 0.889 | Random | 0.960(0.538-1.711) | 77.0% |
| | AA VS.AC + CC | | 2 | 0.843 | 0.390 | Fixed | 0.583(0.170-1.995) | 0.0% |
| rs7804372 | A VS. T | Overall | 4 | 0.000 | 0.408 | Random | 0.876(0.639-1.199) | 86.9% |
| | AA VS. TT | | 4 | 0.002 | 0.606 | Random | 0.857(0.477-1.541) | 80.0% |
| | AT VS. TT | | 4 | 0.007 | 0.173 | Random | 0.806(0.591-1.100) | 75.2% |
| | AA + AT VS.TT | | 4 | 0.001 | 0.263 | Random | 0.822(0.583-1.159) | 82.5% |
| | AA VS.AT + TT | | 4 | 0.005 | 0.791 | Random | 0.931(0.551-1.575) | 76.5% |
| | A VS. T | Chinese | 2 | 0.011 | 0.349 | Random | 0.871(0.651-1.164) | 84.4% |
| | AA VS. TT | | 2 | 0.150 | 0.097 | Random | 0.714(0.480-1.063) | 51.7% |
| | AT VS. TT | | 2 | 0.016 | 0.561 | Random | 0.899(0.628-1.288) | 82.7% |
| | AA + AT VS.TT | | 2 | 0.009 | 0.461 | Random | 0.870(0.601-1.260) | 85.3% |
| | AA VS.AT + TT | | 2 | 0.334 | 0.015 | Fixed | 0.730(0.567-0.940) | 0.0% |
| | A VS. T | Iranian | 2 | 0.000 | 0.734 | Random | 0.841(0.310-2.280) | 93.2% |
| | AA VS. TT | | 2 | 0.006 | 0.957 | Random | 0.958(0.202-4.552) | 86.5% |
| | AT VS. TT | | 2 | 0.020 | 0.306 | Random | 0.648(0.283-1.485) | 81.5% |
| | AA + AT VS.TT | | 2 | 0.001 | 0.263 | Random | 0.722(0.251-2.074) | 90.3% |
| | AA VS.AT + TT | | 2 | 0.022 | 0.842 | Random | 1.137(0.321-4.033) | 80.8% |

When $I^2 \leq 0.25$, variation between studies was only caused by sampling errors, meaning a small heterogeneity; when $I^2$ was between 0.25 and 0.5, moderate heterogeneity was considered; when $I^2 > 0.5$, high heterogeneity was considered; PH: P value of Q test for heterogeneity test; PZ < 0.05 means statistically significant.

carcinogenesis, a large number of studies have been done in the past decade to investigate its roles. Cav-1 regulates multiple cancer-associated processes, such as, cellular transformation, tumor growth, cell death and survival, angiogenesis, cell migration, invasion, apoptosis and metastasis [42]. Cav-1 deficiency has been shown to promote PI3K/AKT, EGFR-MAPK and MAPK signaling in breast cancer [43], and PI3K/AKT/mTOR was shown to be a potential therapeutic target for cancer treatment [10]. In a research studying Kashmiri population, it was found that CAV1 gene mutations (missense and frameshifts) altering tumor suppressive functions in breast cancer resulted in promoting

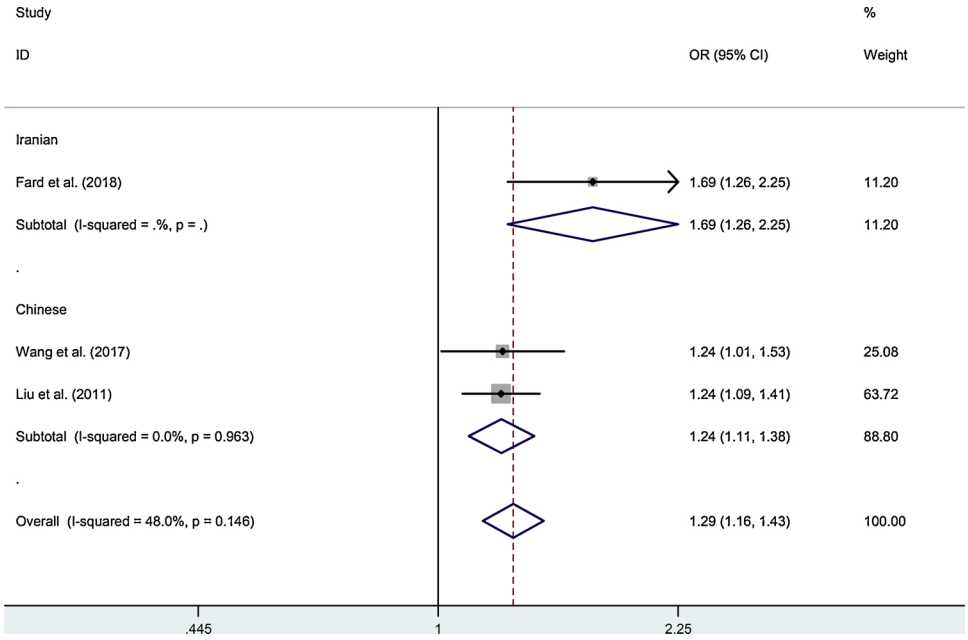


**Fig. 2.** Forest plots of the association between CAV1 rs3807987 (G14713A) polymorphism and breast cancer risk in overall and subgroup analysis of ethnicity in allele comparison (A vs. G).
Each square indicates a study, and the area of the squares is proportional to the weight of the study. The diamond represents the summary OR, and the transverse line means 95% CI. OR = odds ratio, CI = confidence interval.

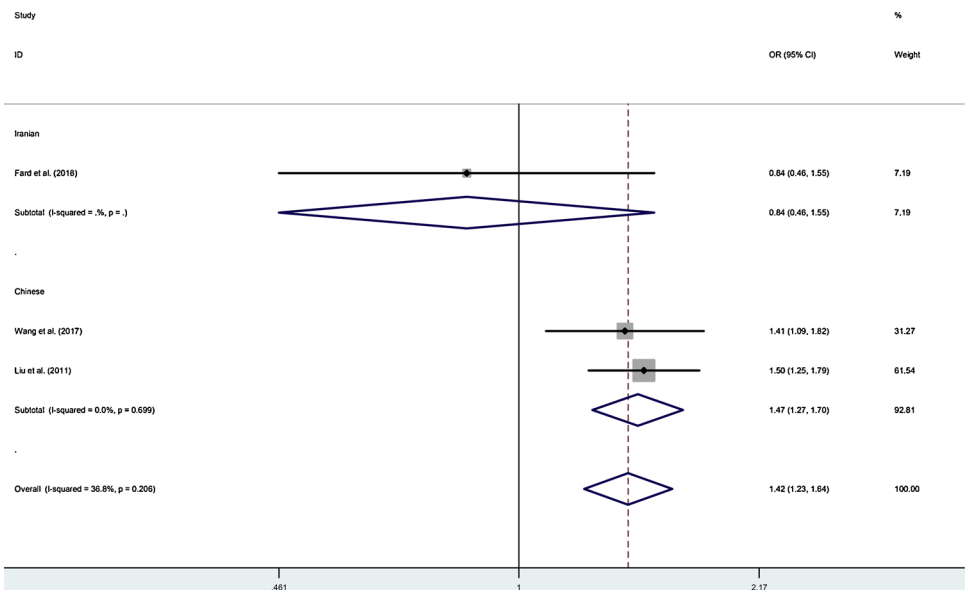


**Fig. 3.** Forest plots of the association between CAV1 rs3807987 (G14713A) polymorphism and breast cancer risk in overall and subgroup analysis of ethnicity in heterozygote comparison (AG vs. GG).
Each square indicates a study, and the area of the squares is proportional to the weight of the study. The diamond represents the summary OR, and the transverse line means 95% CI. OR = odds ratio, CI = confidence interval.

mammary tumorigenesis [44]. Despite the tumor suppressive roles of CAV1 in multiple studies, its expression also increased upon tumor formation in both mouse models and human patients in some other studies [45,46]. In breast cancer, overexpression of CAV1 was shown to be associated with metastasis and poor patient prognosis [47]. As CAV1 being a dual-acting gene in regards to breast cancer [48], meta-analysis can be used as a directional study, and as a reference for the future studies of CAV1. Although previous studies tried to clarify the association between polymorphism of CAV1 and breast cancer risk, the results remained inconclusive [15,16,26,27]. Identification of risk factors for breast cancer might be useful for personalized mammography screening [49]. Thus, it is of great value to explore impact of CAV1 polymorphisms on breast cancer risks. To our best knowledge, this is the first meta-analysis investigating the association between CAV1 polymorphisms and breast cancer.

We found significant associations of CAV1 gene rs3807987 polymorphism with breast cancer risk under the following comparisons: allelic model, heterozygote comparison, and dominant comparison. These findings suggested that individuals with A allele of CAV-1 gene rs3807987 polymorphism might experience a higher susceptibility of breast cancer in overall population and Chinese population. Homozygous GG in a potential recessive pattern might also be associated with decreased risk of breast cancer among overall population and Chinese population. Interestingly, an increased risk was found among Chinese population for heterozygous AG compared to homozygous GG in the heterozygote comparison. This is consistent with its effect on other cancers. For example, in CAV1 gene rs3807987 polymorphism, AG variant genotypes were also shown to be associated with higher liver cancer susceptibility in a research conducted in Asia [50]. CAV1 gene rs3807987 could have similar functions in different cancers, especially among Asian populations.

The presence of A allele of CAV1 gene rs7804372 was found to be protective against the development of nasopharyngeal carcinoma in one study [51]. But in breast cancer, it appears that CAV1 gene rs7804372 polymorphism has different effects in different ethnicities. Among Iranian population, no significant associations between this polymorphism and breast cancer risk was found, while among Chinese population, the homozygous AA was associated with a decreased risk in

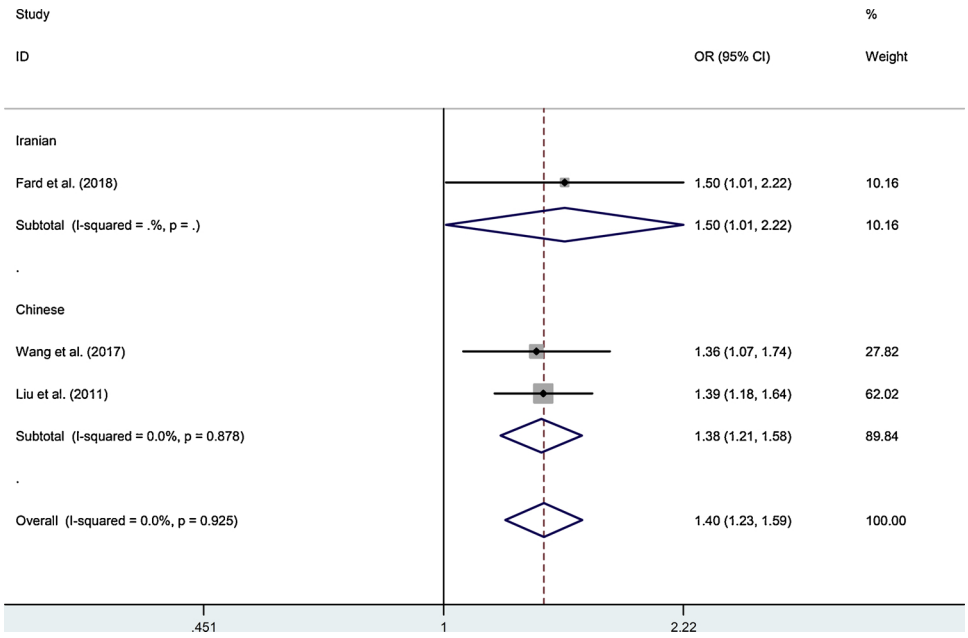


**Fig. 4.** Forest plots of the association between CAV1 rs3807987 (G14713A) polymorphism and breast cancer risk in overall and subgroup analysis of ethnicity in dominant comparison (AA + AG vs. GG).
Each square indicates a study, and the area of the squares is proportional to the weight of the study. The diamond represents the summary OR, and the transverse line means 95% CI. OR = odds ratio, CI = confidence interval.

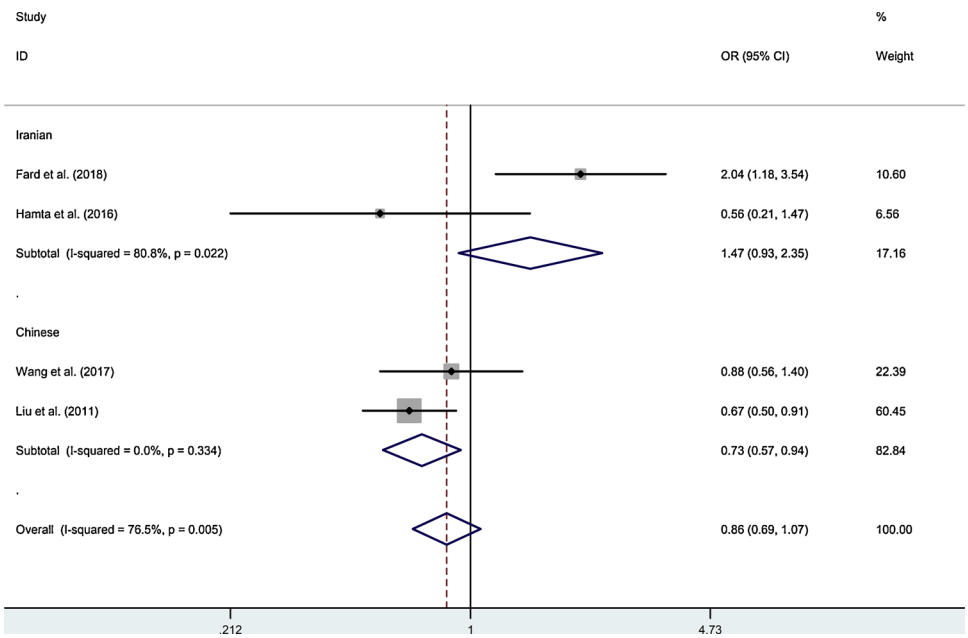


**Fig. 5.** Forest plots of the association between CAV1 rs7804372 (T29107A) polymorphism and breast cancer risk in subgroup analysis of ethnicity in recessive comparison (AA vs. AT + TT).
Each square indicates a study, and the area of the squares is proportional to the weight of the study. The diamond represents the summary OR, and the transverse line means 95% CI. OR = odds ratio, CI = confidence interval.

**Table 3**
Sensitivity analyses for CAV1 polymorphisms and breast cancer susceptibility.

| SNP | Comparison | Effect Model | Estimate (95% Confident Interval) | Effect Model | Estimate (95% Confident Interval) |
|---|---|---|---|---|---|
| rs3807987 | A VS. G | Random | 1.322 (1.127–1.551) | Fixed | 1.288 (1.162–1.428) |
| Overall | AA VS. GG | | 1.317 (0.918–1.891) | | 1.271 (1.024–1.578) |
| | AG VS. GG | | 1.380 (1.125–1.693) | | 1.421 (1.233–1.638) |
| | AA + AG VS.GG | | 1.395 (1.227–1.585) | | 1.395 (1.227–1.585) |
| | AA VS.AG + GG | | 1.234 (0.769–1.980) | | 1.167 (0.946–1.441) |
| rs1997623 | A VS. C | Random | 1.096 (0.716–1.071) | Fixed | 1.130 (0.933–1.369) |
| Overall | AA VS. CC | | 1.306 (0.861–1.981) | | 1.297 (0.858–1.960) |
| | AC VS. CC | | 1.318 (0.674–2.578) | | 1.163 (0.907–1.493) |
| | AA + AC VS.CC | | 1.172 (0.693–1.982) | | 1.150 (0.919–1.438) |
| | AA VS.AC + CC | | 1.092 (0.733–1.628) | | 1.088 (0.731–1.618) |
| rs7804372 | A VS. T | Random | 0.875 (0.639–1.199) | Fixed | 0.855 (0.776– 0.943) |
| Overall | AA VS. TT | | 0.857 (0.476–1.540) | | 0.793 (0.633–0.994) |
| | AT VS. TT | | 0.805 (0.590–1.099) | | 0.828 (0.728–0.942) |
| | AA + AT VS.TT | | 0.821 (0.582–1.158) | | 0.822 (0.728–0.927) |
| | AA VS.AT + TT | | 0.931 (0.550–1.575) | | 0.857 (0.688–1.068) |
| Iranian | A VS. T | Random | 0.841 (0.310–2.280) | Fixed | 0.993 (0.782– 1.260) |
| | AA VS. TT | | 0.958 (0.202–4.552) | | 1.326 (0.820– 2.146) |
| | AT VS. TT | | 0.648 (0.283–1.485) | | 0.708 (0.504–0.996) |
| | AA + AT VS.TT | | 0.722 (0.251–2.074) | | 0.831 (0.610–1.131) |
| | AA VS.AT + TT | | 1.137 (0.321–4.033) | | 1.474 (0.926–2.346) |
| Chinese | A VS. T | Random | 0.871 (0.651–1.163) | Fixed | 0.831 (0.747– 0.924) |
| | AA VS. TT | | 0.714 (0.480–1.063) | | 0.684 (0.529–0.885) |
| | AT VS. TT | | 0.899 (0.628–1.288) | | 0.851 (0.740 –0.978) |
| | AA + AT VS.TT | | 0.870 (0.601–1.260) | | 0.820 (0.719–0.936) |
| | AA VS.AT + TT | | 0.730 (0.567–0.940) | | 0.730 (0.567 –0.940) |

SNP: single nucleotide polymorphism.

the recessive comparison. Based on the available data we included and analyzed, homozygous AA tend to be protective against breast cancer among Chinese population but no impact on breast cancer risk among Iranian people. The slight controversy of the change of the risk between Chinese and Iranian population regarding the CAV1 gene rs7804372 polymorphism could result from either the small number of original studies included for each sub-group analysis or the true difference of genetic predisposition between the two populations.

The sensitivity analyses showed that homozygote comparison (AA vs. GG) of CAV1 gene rs3807987 polymorphism was associated with a significant increase of breast cancer risk for overall population in fixed model, while a non-statistically significant reduction of breast cancer risk was found in random model. In fixed model, CAV1 gene rs7804372 was associated with significant decreases of breast cancer risk for overall population in homozygote comparison (AA vs. TT) and dominant comparison (AA + AT vs. TT), while in random model, these reductions were non-statistically significant. The sensitivity analyses indicated the same trends of either increase or decrease of breast cancer risk in the aforementioned comparisons, with only differences of statistical significance that could be attributed to the relatively small number of studies included.

In the study of rs7804372, we found that there was a high degree of heterogeneity. Further subgroup sensitivity analyses were carried out. The results indicated that heterogeneity in the Iranian subgroup did not alter most of the conclusions. However, in the subgroup of Chinese population, the results showed a change of conclusions, which might be due to the relatively small number of patients and studies included. Therefore, caution should be noted when interpreting the results of

**Table 4**
P values of the Egger's test and Begg's test for CAV1 polymorphism and breast cancer susceptibility.

| SNP | Subgroup | Egger's test P > \|t\| | Begg's test P > \|z\| |
|---|---|---|---|
| rs3807987 | A VS. G | 0.382 | 0.296 |
| | AA VS. GG | 0.762 | 1.000 |
| | AG VS. GG | 0.052 | 0.296 |
| | AA + AG VS.GG | 0.569 | 1.000 |
| | AA VS.AG + GG | 0.751 | 1.000 |
| rs1997623 | A VS. C | 0.633 | 1.000 |
| | AA VS. CC | 0.089 | 1.000 |
| | AC VS. CC | 0.108 | 0.296 |
| | AA + AC VS.CC | 0.569 | 1.000 |
| | AA VS.AC + CC | 0.106 | 1.000 |
| rs7804372 | A VS. T | 0.690 | 0.734 |
| | AA VS. TT | 0.638 | 0.734 |
| | AT VS. TT | 0.950 | 1.000 |
| | AA + AT VS.TT | 0.806 | 1.000 |
| | AA VS.AT + TT | 0.641 | 0.734 |

Chinese subgroup in rs7804372. For rs3807987 and rs1997623, the results of sensitivity analyses demonstrated no change of conclusions when different effect models were applied. Therefore, the conclusions are relatively robust.

However, our research still had several limitations. First, the populations included in the original studies were Iranian and Chinese populations; therefore, it might not be a good representation of populations in other areas. Second, significant heterogeneity and publication bias were observed in some of the overall comparisons and subgroup analyses. Subgroup analysis showed that ethnicity could be one of the sources of heterogeneity. Additionally, some of the original studies did not clarify their criteria for a breast cancer diagnosis, which might contribute to heterogeneity. Third, confounding factors such as age, gender, weight, smoking, and drinking status were not analyzed as we were unable to retrieve those detailed information from the original studies for analysis. So we were unable to further assess the potential gene-environment interactions. Fourth, the analysis could not be stratified by breast cancer stage, the time of diagnosis, and treatment option (i.e., surgery, endocrine therapy, or chemotherapy) detailed information on these variables were not sufficient in the included original studies. Last, the number of studies included in our meta-analysis was low, and more research for impact of CAV1 gene polymorphisms on breast cancer risk is needed.

In conclusion, we discovered that rs3807987 and rs7804372 polymorphism in CAV1 gene rendered a change of breast cancer risk, while rs1997623 has no association with breast cancer risk. The presence of allelic A in rs3807987 could be a risk factor of breast cancer. Homozygous AA in rs7804372 polymorphism might be one of the genetic factors conferring protective impact on breast cancer for Chinese. To confirm the associations, more well-designed and large studies in various populations are needed.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2019.152518.

## References


[1] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, CA Cancer J. Clin. 65 (2015) 87–108.
[2] L.A. Torre, F. Islami, R.L. Siege, E.M. Ward, A. Jemal, Global cancer in women: burden and trends, Cancer Epidemiol. Biomarkers. Prev. 26 (2017) 444–457.
[3] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, CA Cancer J. Clin. 68 (2018) (2018) 7–30.
[4] Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease, Lancet 358 (2001) 1389–1399.
[5] D.S. Tan, C. Marchio, J.S. Reis-Filho, Hereditary breast cancer: from molecular pathology to tailored therapies, J. Clin. Pathol. 61 (2008) 1073–1082.
[6] I. Mercier, M.P. Lisanti, Caveolin-1 and breast cancer: a new clinical perspective, Adv. Exp. Med. Biol. 792 (2012) 83–94.
[7] J.A. Engelman, X.L. Zhang, F. Galbiati, M.P. Lisanti, Chromosomal localization, genomic organization, and developmental expression of the murine caveolin gene family (Cav-1, -2, and -3). Cav-1 and Cav-2 genes map to a known tumor suppressor locus (6-A2/7q31), FEBS Lett. 429 (1998) 330–336.
[8] N. Patani, L.A. Martin, J.S. Reis-Filho, M. Dowsett, The role of caveolin-1 in human breast cancer, Breast. Cancer. Res. Treat. 131 (2012) 1–15.
[9] S. Fan, J. Meng, L. Zhang, X. Zhang, C. Liang, CAV1 polymorphisms rs1049334, rs1049337, rs7804372 might be the potential risk in tumorigenicity of urinary cancer: a systematic review and meta-analysis, Pathol. Res. Pract. 215 (2019) 151–158.
[10] R. Gupta, C. Toufaily, B. Annabi, Caveolin and cavin family members: dual roles in cancer, Biochimie 107 (2014) 188–202.
[11] T.M. Williams, G.S. Hassan, J. Li, A.W. Cohen, F. Medina, P.G. Frank, R.G. Pestell, D. Di Vizio, M. Loda, M.P. Lisanti, Caveolin-1 promotes tumor progression in an autochthonous mouse model of prostate cancer: genetic ablation of Cav-1 delays advanced prostate tumor development in tramp mice, J. Biol. Chem. 280 (2005) 25134–25145.
[12] T. Li, F. Sotgia, M.A. Vuolo, M. Li, W.C. Yang, R.G. Pestell, J.A. Sparano, M.P. Lisanti, Caveolin-1 mutations in human breast cancer: functional association with estrogen receptor alpha positive status, Am. J. Pathol. 168 (2006) 1998–2013.
[13] M.N. Aoki, M.K. Amarante, J.M. Oda, M.A. Watanabe, Caveolin involvement and modulation in breast cancer, Mini Rev. Med. Chem. 11 (2011) 1143–1152.
[14] S.T. Chen, S.Y. Lin, K.T. Yeh, S.J. Kuo, W.L. Chan, Y.P. Chu, J.G. Chang, Mutational, epigenetic and expressional analyses of caveolin-1 gene in breast cancers, Int. J. Mol. Med. 14 (2004) 577–582.
[15] L.C. Liu, C.H. Su, H.C. Wang, C.W. Tsai, W.S. Chang, C.Y. Ho, C.I. Wu, F.J. Li, C.H. Lin, H.Y. Lane, D.T. Bau, Significant association of caveolin-1 (CAV1) genotypes with breast cancer in Taiwan, Anticancer Res. 31 (2011) 3511–3555.
[16] M. Wang, T. Tian, X. Ma, W. Zhu, Y. Guo, Z. Duan, J. Fan, S. Lin, K. Liu, Y. Zheng, Q. Sheng, Z.J. Dai, H. Peng, Genetic polymorphisms in caveolin-1 associate with breast cancer risk in Chinese Han population, Oncotarget 9 (2017) 91654–91661.
[17] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P. Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (2009) 264–269 W64.
[18] G.A. Wells, B. Shea, D. O'Connell, J. Peterson, V. Welch, M. Losos, P. Tugwell, The Newcastle-OttawaScale (NOS) for Assessing the Quality If Nonrandomized Studies in Meta-Analyses, Ottawa Hospital Research Institute, 2009 (Accessed 28 February 2019), http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[19] W.J. Gu, F. Wang, L. Tang, J.C. Liu, Single-dose etomidate does not increase mortality in patients with sepsis: a systematic review and meta-analysis of randomized controlled trials and observational studies, Chest 147 (2015) 335–346.
[20] S. Alizadeh, K. Djafarian, S. Moradi, S. Shab-Bidar, C667T and A1298C polymorphisms of methylenetetrahydrofolate reductase gene and susceptibility to myocardial infarction: a systematic review and meta-analysis, Int. J. Cardiol. 217 (2016) 99–108.
[21] F. Wang, Y. Wang, T. Sun, H.L. Yu, Hyperbaric oxygen therapy for the treatment of traumatic brain injury: a meta-analysis, Neurol. Sci. 37 (2016) 693–701.
[22] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Cochrane Handbookfor Systematic Reviews of Interventions Version 5.1.0, The Cochrane Collaboration, 2011.
[23] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ 327 (2003) 557–560.
[24] R. DerSimonian, N. Laird, Meta-analysis in clinical trials revisited, Contemp. Clin. Trials 45 (2015) 139–145.
[25] W. Jia, X. Qi, Q. Li, Association between Rs3807989 polymorphism in Caveolin-1 (CAV1) gene and atrial fibrillation: a meta-analysis, Med. Sci. Monit. 22 (2016) 3961–3966.
[26] Z.T. Fard, N. Nafisi, The relationship between 6 polymorphisms of Caveolin-1 gene and the risk of breast cancer, Clin. Breast Cancer 18 (2018) e893–e898.
[27] A. Hamta, G. Maryam, K. Sedigheh, Genotypic frequency of Caveolin-1 (CAV1) T29107A polymorphism in the Iranian patients with breast cancer, J. Kermanshah. Univ. Med. Sci. 20 (2016) 79–83.
[28] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[29] F. Sotgia, U.E. Martinez-Outschoorn, A. Howell, R.G. Pestell, S. Pavlides, M.P. Lisanti, Caveolin-1 and cancer metabolism in the tumor microenvironment: markers, models, and mechanisms, Annu. Rev. Pathol. 7 (2012) 423–467.
[30] J.H. Chidlo Jr., W.C. Sessa, Caveolae, caveolins, and cavins: complex control of cellular signalling and inflammation, Cardiovasc. Res. 86 (2010) 219–225.
[31] H. Xu, L. Zhang, W. Chen, J. Xu, R. Zhang, R. Liu, L. Zhou, W. Hu, R. Ju, C. Lee, W. Lu, A. Kumar, X. Li, Z. Tang, Inhibitory effect of caveolin-1 in vascular endothelial cells, pericytes and smooth muscle cells, Oncotarget 8 (2017) 76165–76173.
[32] H. Yang, L. Guan, S. Li, Y. Jiang, N. Xiong, L. Li, C. Wu, H. Zeng, Y. Liu, Mechanosensitive caveolin-1 activation-induced PI3K/Akt/mTOR signaling pathway promotes breast cancer motility, invadopodia formation and metastasis in vivo, Oncotarget 7 (2016) 16227–16247.
[33] S.M. El-Gendi, M.F. Mostafa, A.M. El-Gend, Stromal caveolin-1 expression in breast carcinoma. Correlation with early tumor recurrence and clinical outcome, Pathol. Oncol. Res. 18 (2012) 459–469.
[34] Z.D. Nassar, M.M. Hill, R.G. Parton, M.O. Parat, Caveola-forming proteins caveolin-1 and PTRF in prostate cancer, Nat. Rev. Urol. 10 (2013) 529–536.
[35] G. Ayala, M. Morello, A. Frolov, S. You, R. Li, F. Rosati, G. Bartolucci, G. Danza,

R.M. Adam, T.C. Thompson, M.P. Lisanti, M.R. Freeman, D.D. Vizio, Loss of caveolin-1 in prostate cancer stroma correlates with reduced relapse-free survival and is functionally relevant to tumour progression, J. Pathol. 231 (2013) 77–87.
[36] M.R. Freeman, W. Yang, D. Di Vizio, Caveolin-1 and prostate cancer progression, Adv. Exp. Med. Biol. 729 (2012) 95–110.
[37] P. Fu, F. Chen, Q. Pan, X. Zhao, C. Zhao, W.C. Cho, H. Chen, The different functions and clinical significances of caveolin-1 in human adenocarcinoma and squamous cell carcinoma, Onco Targets Ther. 10 (2017) 819–835.
[38] H.L. Chen, L.F. Fan, J. Gao, J.P. Ouyang, Y.X. Zhang, Differential expression and function of the caveolin-1 gene in non-small cell lung carcinoma, Oncol. Rep. 25 (2011) 359–366.
[39] P. Cassoni, L. Daniele, E. Maldi, L. Righi, V. Tavaglione, S. Novello, M. Volante, G.V. Scagliotti, M. Papotti, Caveolin-1 expression in lung carcinoma varies according to tumour histotype and is acquired de novo in brain metastases, Histopathology 55 (2009) 20–27.
[40] T. Kato, M. Miyamoto, K. Kato, Y. Cho, T. Itoh, T. Morikawa, S. Okushiba, S. Kondo, T. Ohbuchi, H. Katoh, Difference of caveolin-1 expression pattern in human lung neoplastic tissue. Atypical adenomatous hyperplasia, adenocarcinoma and squamous cell carcinoma, Cancer. Lett. 214 (2004) 121–128.
[41] R. Senetta, G. Stella, E. Pozzi, N. Sturli, D. Massi, P. Cassoni, Caveolin-1 as a promoter of tumour spreading: when, how, where and why, J. Cell. Mol. Med. 17 (2013) 325–336.
[42] M. Sainz-Jaspeado, J. Martin-Liberal, L. Lagares-Tena, S. Mateo-Lozano, X. Garcia del Muro, O.M. Tirado, Caveolin-1 in sarcomas: friend or foe? Oncotarget 2 (2011) 305e312.
[43] S. Feng, Y. Wang, X. Wang, Z. Wang, Y. Cui, J. Liu, C. Zhao, M. Jin, W. Zou, Caveolin-1 gene silencing promotes the activation of PI3K/AKT dependent on Eralpha 36 and the transformation of MCF10ACE, Sci. China Life Sci. 53 (2010) 598e605.
[44] N. Syeed, S.A. Husain, S. Abdullah, A.S. Sameer, N.A. Chowdri, M.S. Nanda, M.A. Siddiqi, Mutational profile of the CAV-1 gene in breast cancer cases in the ethnic Kashmiri population, Asian Pac. J. Cancer Prev. 11 (2010) 1099e1105.
[45] G. Yang, L.D. Truong, T.L. Timme, C. Ren, T.M. Wheeler, S.H. Park, Y. Nasu, C.H. Bangma, M.W. Kattan, P.T. Scardino, T.C. Thompson, Elevated expression of caveolin is associated with prostate and breast cancer, Clin. Cancer Res. 4 (1998) 1873e1880.
[46] K.H. Nam, B.L. Lee, J.H. Park, J. Kim, N. Han, H.E. Lee, M.A. Kim, H.S. Lee, W.H. Kim, Caveolin 1 expression correlates with poor prognosis and focal adhesion kinase expression in gastric cancer, Pathobiology 80 (2013) 87e94.
[47] S. Garcia, J.P. Dales, E. Charafe-Jauffret, S. Carpentier-Meunier, L. Andrac-Meyer, J. Jacquemier, C. Andonian, M.N. Lavaut, C. Allasia, P. Bonnier, C. Charpin, Poor prognosis in breast carcinomas correlates with increased expression of targetable CD146 and c-Met and with proteomic basal-like phenotype, Hum. Pathol. 38 (2007) 830e841.
[48] I. Mercier, M.P. Lisanti, Caveolin-1 and breast cancer: a new clinical perspective, Adv. Exp. Med. Bio. 729 (2012) 83–94.
[49] H.D. Nelson, B. Zakher, A. Cantor, R. Fu, J. Griffin, E.S. O`Meara, D.S. Buist, K. Kerlikowske, N.T. van Ravesteyn, A. Trentham-Dietz, J.S. Mandelblatt, D.L. Miglioretti, Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis, Ann. Intern. Med. 156 (2012) 635–648.
[50] C.M. Hsu, M.D. Yang, C.W. Tsai, C.Y. Ho, W.S. Chang, S.C. Chang, L.B. Jeng, Y. Tsai, F.J. Tsai, D.T. Bau, The contribution of caveolin-1 genotype and phenotype to hepatocellular carcinoma, Anticancer Res. 33 (2013) 671e677.
[51] D.T. Bau, M.H. Tsai, Y.A. Tsou, C.H. Wang, C.W. Tsai, S.S. Sun, C.H. Hua, S.K. Shyue, R.Y. Tsai, The association of caveolin-1 genotypes with oral cancer susceptibility in Taiwan, Ann. Surg. Oncol. 18 (2011) e1431–e1438.