Prognostic role of caveolin in breast cancer: A meta-analysis

Ma X et al., Prognostic role of caveolin in breast cancer: A meta-analysis The Breast (2013)

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Outline

* Background
* Materials & methods
* Results & Discussion
* Conclusion

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Background

1. Breast cancer

* Most frequently diagnosed cancer and the leading cause of cancer death in females worldwide.
* Accounting for 23% (1.38 million) of the total new cancer cases & 14% (458,400) of the total cancer deaths.
* Recurrence rate is high, eg:

  Triple-negative breast cancer (TNBC): 34%

Jemal A. Global cancer statistics. CA Cancer J Clin(2011)

Background

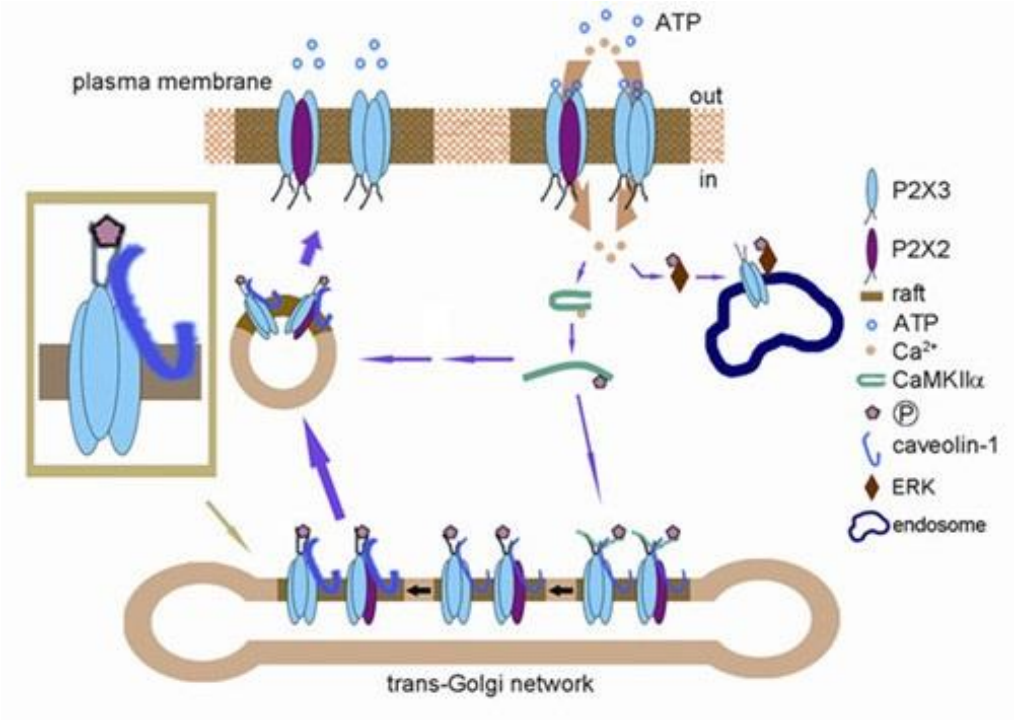
1. Breast cancer

* Biomarkers: p53 mutation, cyclin E, BRCA1 methylation...
* A heatedly studied biomarker recently: caveolin (Cav)

Background

2. Caveolin

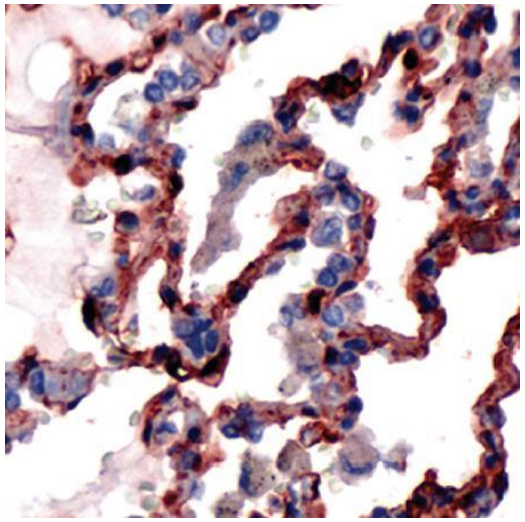
* Integral membrane protein in mesenchymal cells, such as adipocytes, endothelial cells, and fibroblasts.



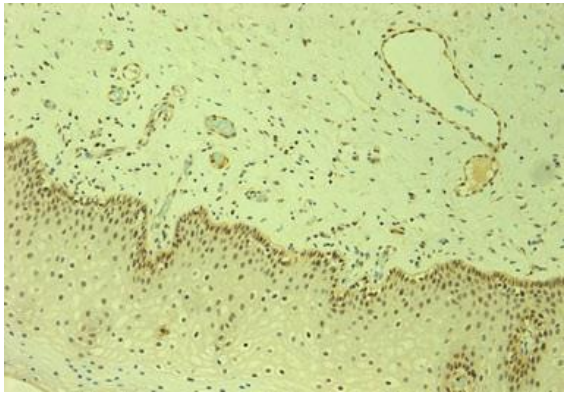
Membrane organizing centers

Background

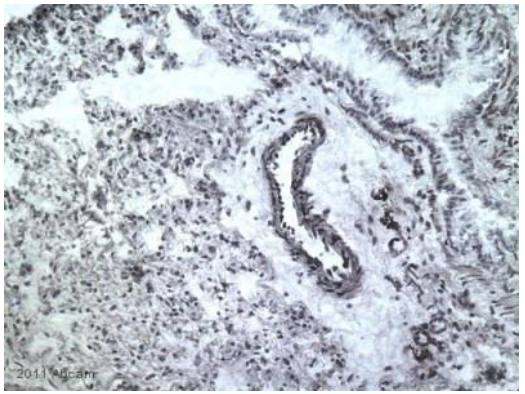
2. Caveolin family:



Cav-1



Cav-2



Cav-3

Background

2. Caveolin

* Nam KH. Caveolin 1 expression correlates with poor prognosis and focal adhesion kinase expression in **gastric cancer**. Pathobiology (2013)
* Tang Y.Caveolin-1 is related to invasion, survival, and poor prognosis in **hepatocellular cancer**. Med Oncol (2012)
* Steffens S. Caveolin 1 protein expression in **renal cell carcinoma** predicts survival. BMC Urol (2011)
* Others： atherosclerosis, restrictive lung disease, pulmonary fibrosis, cardiomyopathy, muscular dystrophy, and bladder dysfunction.

Background

3. Caveolin & breast cancer

* Recently, both the epithelial and stromal caveolin have been detected in breast cancer patients to determine the prognosis.
* In vitro studies have shown that both stromal and epithelial Cav-1 play a protective role against mammary hyperplasia and tumor genesis in breast cancer.

* Williams TM. Stromal and epithelial caveolin-1 both confer a protective effect against mammary hyperplasia and tumorigenesis: caveolin-1 antagonizes cyclin D1 function in mammary epithelial cells.Am J Pathol(2006)

Background

3. Caveolin & breast cancer

* However, the prognostic role of stromal and epithelial Cav-1 varied in many clinical studies.

* Liedtke C. Caveolin-1 expression in benign and malignant lesions of the breast.World J Surg Oncol(2007)
* Qian N.Prognostic significance of tumor/stromal caveolin-1 expression in breast cancerpatients.Cancer Sci(2011)

Background

4. Aim of this study

* To clarify whether caveolin could be a prognostic factor for patients with breast cancer.

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Materials & methods

1. Search strategy

* Database: Pubmed and EMBASE
* Search on April 26, 2012
* Keywords: “caveolin”, “breast cancer”, “prognosis”

Materials & methods

2. Study inclusion criteria

* (i) patients with breast cancer
* (ii) the expression of caveolin in tumor epithelial or stromal cells was measured
* (iii) the association between caveolin expression and survival outcome (OS/CSS/PFS/DFS) was analyzed

Materials & methods

3. Study exclusion criteria

* (i) review, letter or experiment on animal models
* (ii) not patients with breast cancer
* (iii) not about caveolin expression
* (iv) lacked key information for hazard ratio (HR) estimation analysis

Materials & methods

4. Data extraction

* Article review & Data extraction: two investigators.
* (i) Baseline characteristics
* (ii) Survival outcomes (the Kaplane-Meier survival curves and p values **OR** Hazard ratios (HR) and 95% confidence interval (CI))

Materials & methods

5. Statistical analysis

* Aggregation of the survival results: logHR and Standard errors (SE)
* Subgroup analysis
* Forrest plots
* An observed HR>1 indicated a worse outcome
* Software: RevMan 5.1 & STATA 11.0

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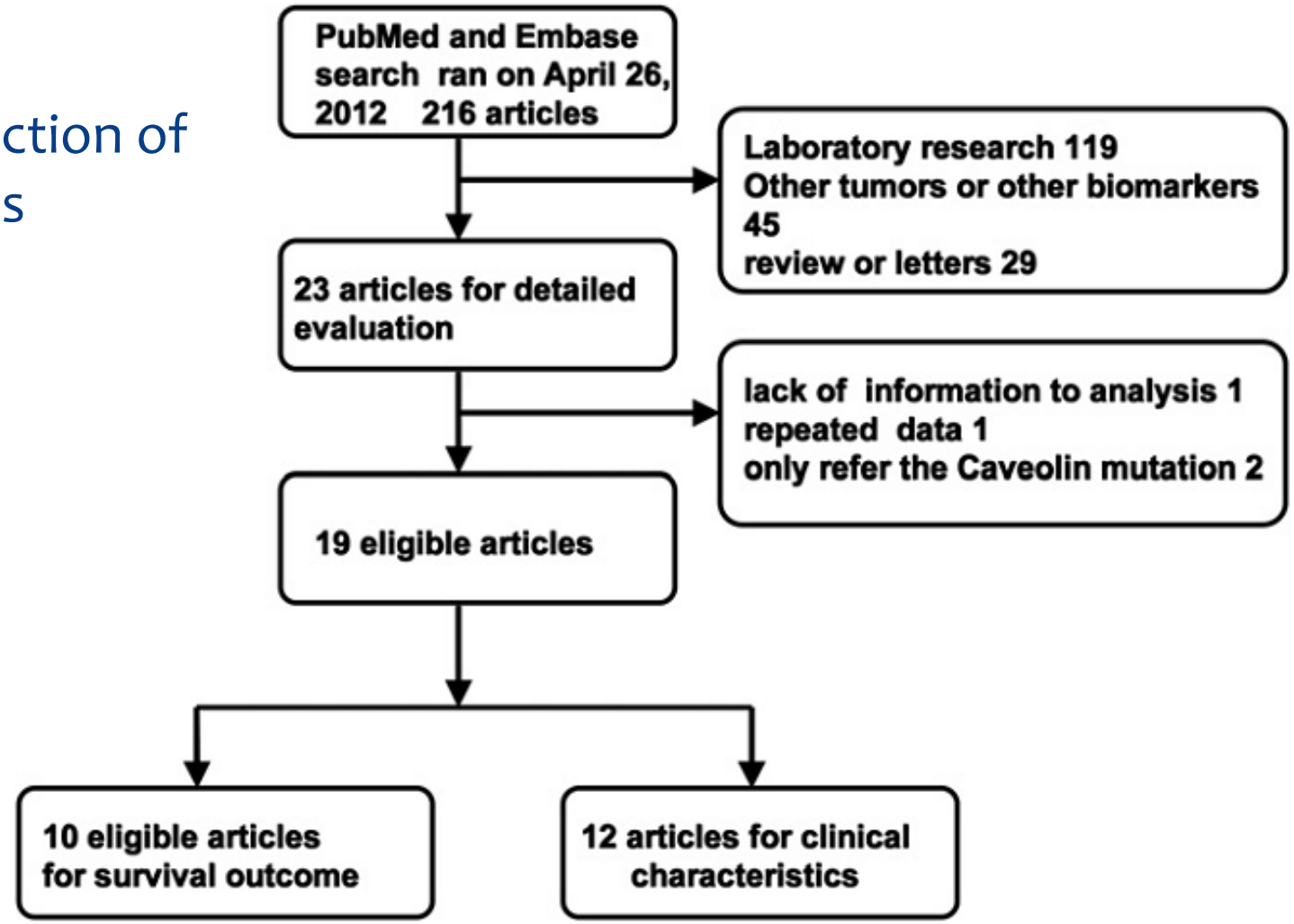
Results & Discussion

1. Selection of studies



Results & Discussion

2. Baseline characteristics-1

Author	Date	N	Age	Positive site	Tumor type	III & IV %	Follow-up
Witkiewicz AK	2010	85	NR	epithelial and stroma	TNBC and BLBC	79.3	33.8months
Witkiewicz AK 2	2009	78	NR	stroma	invasive breast cancer	NR	146.8months
Witkiewicz AK 3	2009	154	59.5	epithelial and stroma	breast cancer	11.4	100.8months
El-Gendi SM	2011	91	50.13	epithelial and stroma	NR	68.2	21.94months
Koo JS	2011	722	NR	epithelial and stroma	invasive breast cancer	21.7	71 months
Liedtke C	2007	109	NR	epithelial	invasive breast cancer	40.4	82 months
Qian N	2011	86	NR	epithelial and stroma	invasive breast cancer	NR	74 months
Savage K (Breakthrough)	2008	210	NR	epithelial	invasive breast cancer	63.1	67 months
Savage K (Vancouvor)	2008	310	NR	epithelial	invasive breast cancer	24.6	129.6 months
Savage K 2	2007	245	NR	epithelial	invasive breast carcinomas	61.7	67 months
Elsheikh SE	2008	516	NR	epithelial	invasive breast cancer	50.1	NR
Sloan EK	2009	173	54	epithelial and stroma	invasive breast carcinoma	18.2	146.8 months
Charpin C	2009	924	NR	epithelial	invasive breast carcinomas	NR	79 month
Garcia S	2007	930	54.2	epithelial	invasive ductal carcinomas	33.3	78 months
Joshi B	2008	438	NR	epithelial	invasive breast carcinoma	NR	180 months
Mercier I	2009	28	NR	epithelial	NR	NR	NR
Park SS	2005	130	NR	epithelial	invasive ductal carcinoma	46.9	NR
Pinilla SM	2006	496	NR	epithelial	invasive breast carcinoma	44.9	NR
Sagara Y	2004	162	55	epithelial	breast cancer	NR	41 months
Yang G	1998	39	NR	epithelial	invasive breast carcinoma	NR	NR

Results & Discussion

2. Baseline characteristics-2

Author	Type	Antibody	Dilution	Method	Cut-off value	Survial outcome
Witkiewicz AK	Cav-1	rabbit polyclonal anti-Cav-1, BD	1/4000	IHC	no staining	OS
Witkiewicz AK 2	Cav-1	mouse monoclonal anti-Cav-1, BD	1/50	IHC	30% staining	RFS
Witkiewicz AK 3	Cav-1	rabbit polyclonal anti-Cav-1, Santa Cruz	1/500	IHC	no staining	PFS
El-Gendi SM	Cav-1	rabbit monoclonal anti-Cav-1, Abcam	1/100	IHC	no staining	PFS
Koo JS	Cav-1, Cav-2 and Cav-3	monoclonal anti-Cav-1, BD; anti-Cav-2, Abcam; polyclonal anti-Cav-3, Abcam	1/50,1/200 and 1/100	TMA	30% staining	OS DFS
Liedtke C	Cav-1	mouse monoclonal anti-Cav-1, BD	1/200	TMA	no staining	OS DFS
Qian N	Cav-1	monoclonal anti-Cav-1,Cell Signaling	1/800	IHC	5% staining	DFS
Savage K (Breakthrough)	Cav-1 and Cav-2	mouse monoclonal anti-Cav-2, BD	1/100	TMA	no staining	CSS
Savage K (Vancouvor)	Cav-1 and Cav-2	mouse monoclonal anti-Cav-2, BD	1/100	TMA	no staining	CSS
Savage K 2	Cav-1	mouse monoclonal anti-Cav-1, Santa Cruz	1/10,000	IHC	scores = 4	OS DFS
Elsheikh SE	Cav-1 and Cav-2	mouse monoclonal antibodies, BD	1/150 and 1/50	TMA	no staining	DFS MFS CSS
Sloan EK	Cav-1	mouse monoclonal anti-Cav-1, BD	1/50	IHC	no staining	OS
Charpin C	Cav-1	rabbit polycolonal anti-Cav-1, Santa Cruz	NR	TMA	NR	DFS
Garcia S	Cav-1	rabbit polyclonal anti-Cav-1, Santa Cruz	1:50	TMA	no staining	DFS
Joshi B	Cav-1	mouse anti-Cav-1, Transduction	NR	TMA	25% staining	DFS
Mercier I	Cav-1	rabbit monoclonal anti-Cav-1, Santa Cruz	1/100	IHC and DNA	NR	NR
Park SS	Cav-1	monoclonal anti-Cav-1, Santa Cruz	1/400	IHC	score = 6	NR
Pinilla SM	Cav-1	mouse monoclonal anti-Cav-1, BD	1/10,	TMA	no staining	NR
Sagara Y	Cav-1 and Cav-2	anti-Cav-1,BD; anti-Cav-2, Santa Cruz	1/2,	RTPCR	NR	DFS
Yang G	Cav-1	rabbit polyclonal anti-Cav-1, Transduction	1/400	IHC	no staining	NR

Results & Discussion

* 3. Caveolin & Survival outcome

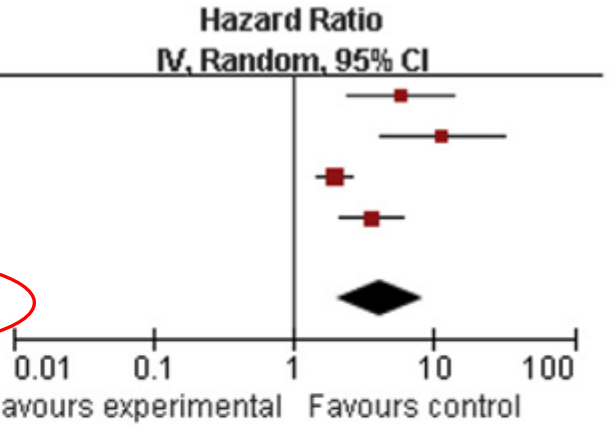
  3.1 stromal Cav-1 (A: OS B: DFS/PFS)

A

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Koo JS 2011	1.76	0.45	21.6%	5.81 [2.41, 14.04]
Sloan EK 2009	2.43	0.52	19.3%	11.36 [4.10, 31.47]
Witkiewicz AK 2010	0.6657	0.15	31.1%	1.95 [1.45, 2.61]
Witkiewicz AK* 2010	1.28	0.26	28.0%	3.60 [2.16, 5.99]
Total (95% CI)			**100.0%**	**4.12 [2.05, 8.28]**

Heterogeneity: Tau² = 0.39; Chi² = 16.50, df = 3 (P = 0.0009); I² = 82%

Test for overall effect: Z = 3.97 (P < 0.0001)

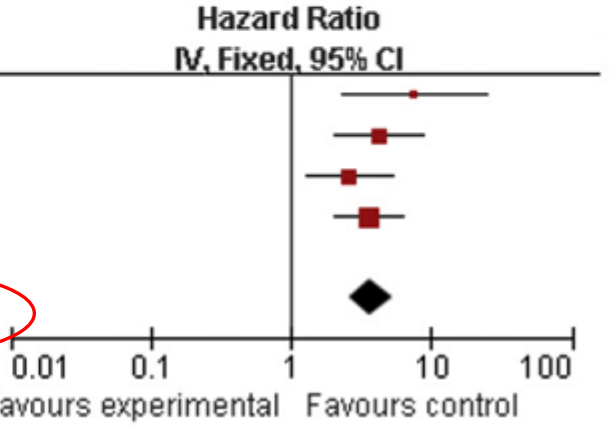


B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
El-Gendi SM 2011	2.01	0.61	9.3%	7.46 [2.26, 24.67]
Koo JS 2011	1.45	0.37	25.2%	4.26 [2.06, 8.80]
Qian N 2011	0.96	0.37	25.2%	2.61 [1.26, 5.39]
Witkiewicz AK 3 2009	1.2723	0.292	40.4%	3.57 [2.01, 6.33]
Total (95% CI)			**100.0%**	**3.69 [2.57, 5.31]**

Heterogeneity: Chi² = 2.37, df = 3 (P = 0.50); I² = 0%

Test for overall effect: Z = 7.04 (P < 0.00001)



Results & Discussion

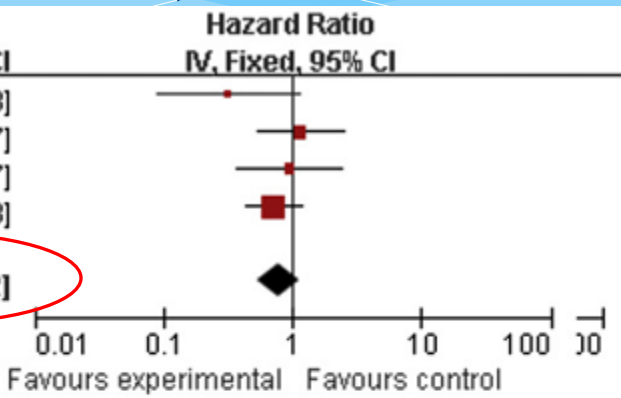
* 3. Caveolin & Survival outcome

3.2 tumor epithelial Cav-1 (C: OS D: DFS/PFS)

C

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Koo JS 2011	-1.15	0.65	8.4%	0.32 [0.09, 1.13]
Liedtke C 2007	0.14	0.39	23.3%	1.15 [0.54, 2.47]
Sloan EK 2009	-0.06	0.47	16.0%	0.94 [0.37, 2.37]
Witkiewicz AK 2010	-0.34	0.26	52.3%	0.71 [0.43, 1.18]
Total (95% CI)			**100.0%**	**0.78 [0.54, 1.12]**

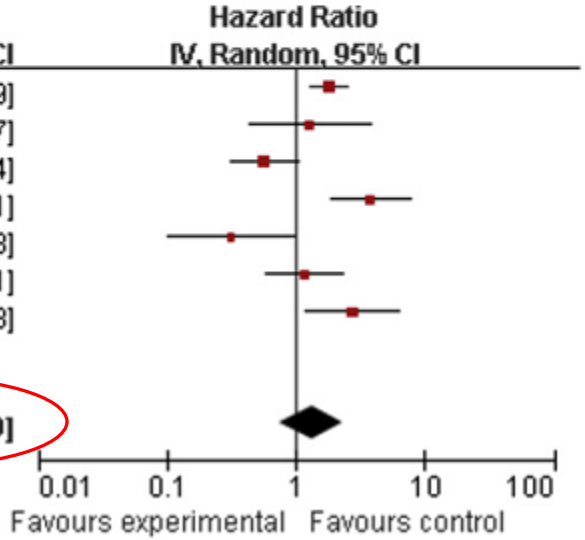
Heterogeneity: Chi² = 3.20, df = 3 (P = 0.36); I² = 6%
Test for overall effect: Z = 1.34 (P = 0.18)



D

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Charpin C 2009	0.58	0.17	18.4%	1.79 [1.28, 2.49]
El-Gendi SM 2011	0.25	0.55	11.3%	1.28 [0.44, 3.77]
Elsheikh SE 2008	-0.57	0.31	16.0%	0.57 [0.31, 1.04]
Joshi B 2008	1.33	0.37	14.8%	3.78 [1.83, 7.81]
Koo JS 2011	-1.16	0.58	10.8%	0.31 [0.10, 0.98]
Liedtke C 2007	0.15	0.35	15.2%	1.16 [0.59, 2.31]
Qian N 2011	1.01	0.43	13.6%	2.75 [1.18, 6.38]
Total (95% CI)			**100.0%**	**1.32 [0.76, 2.29]**

Heterogeneity: Tau² = 0.41; Chi² = 27.05, df = 6 (P = 0.0001); I² = 78%
Test for overall effect: Z = 0.97 (P = 0.33)



Results & Discussion

3. Caveolin & Survival outcome

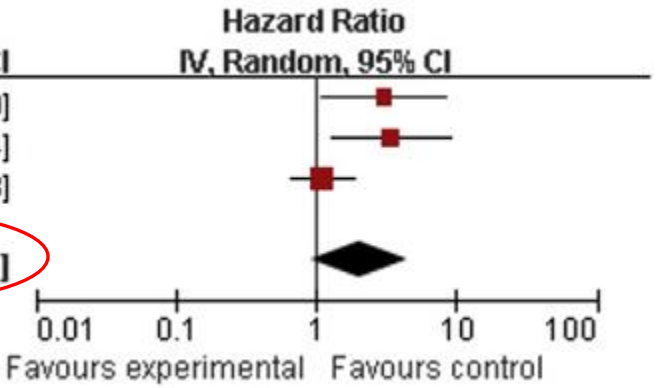
3.3 tumor epithelial Cav-2 (E: CSS)

E

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Elsheikh SE 2008	1.12	0.52	28.3%	3.06 [1.11, 8.49]
Savage K 2008	1.21	0.5	29.3%	3.35 [1.26, 8.94]
Savage K* 2008	0.1	0.27	42.4%	1.11 [0.65, 1.88]
Total (95% CI)			**100.0%**	**2.04 [0.91, 4.56]**

Heterogeneity: Tau² = 0.32; Chi² = 5.63, df = 2 (P = 0.06); I² = 64%

Test for overall effect: Z = 1.74 (P = 0.08)



Results & Discussion

3. Caveolin & Survival outcome – summary

Type	Pos.	Outcome	Method	*N*	Patients	Model	HR (95% CI)	*p*-value	Heterogeneity (I^2, *p*)	Conclusion
Cav-1	stromal	OS	total	4	980	Random	4.12 [2.05, 8.28]	<0.0001	82%, 0.0009	positive
			TMA	1	722	–	5.81 [2.41, 14.04]	<0.0001	–	positive
			IHC	3	258	Random	3.76 [1.68, 8.39]	0.001	85%, 0.001	positive
		DFS/PFS	total	4	1053	Fixed	3.69 [2.57, 5.31]	<0.00001	0%, 0.50	positive
			TMA	1	722	–	4.26 [2.06, 8.80]	<0.0001	–	positive
			IHC	3	331	Fixed	3.52 [2.31, 5.36]	<0.00001	8%, 0.34	positive
	epithelial	OS	total	4	1089	Fixed	0.78 [0.54, 1.12]	0.18	6%, 0.36	negative
			TMA	2	831	Random	0.67 [0.19, 2.33]	0.53	65%, 0.09	negative
			IHC	2	258	Fixed	0.76 [0.49, 1.19]	0.23	0%, 0.60	negative
		DFS/PFS	total	7	2886	Random	1.32 [0.76, 2.29]	0.33	78%, 0.0001	negative
			TMA	5	2709	Random	1.15 [0.57, 2.31]	0.7	84%, <0.0001	negative
			IHC	2	177	Fixed	2.06 [1.06, 4.00]	0.03	16%, 0.28	positive
Cav-2	epithelial	CSS	total	3	761	Random	2.04 [0.91, 4.56]	0.08	64%, 0.06	negative

Negative expression of stromal Cav-1 was associated with poor prognosis of breast cancer, while the detection of Cav-1 and Cav-2 in tumor epithelial cells was not.

Results & Discussion

4. Assessment of publication bias

Begg's funnel plot and test

Type	p value
stromal Cav-1--OS	0.042
stromal Cav-1--DFS/PFS	0.497
epithelial Cav-1--OS	0.497
epithelial Cav-1--DFS/PFS	0.652
epithelial Cav-2--CSS	0.602

Results & Discussion

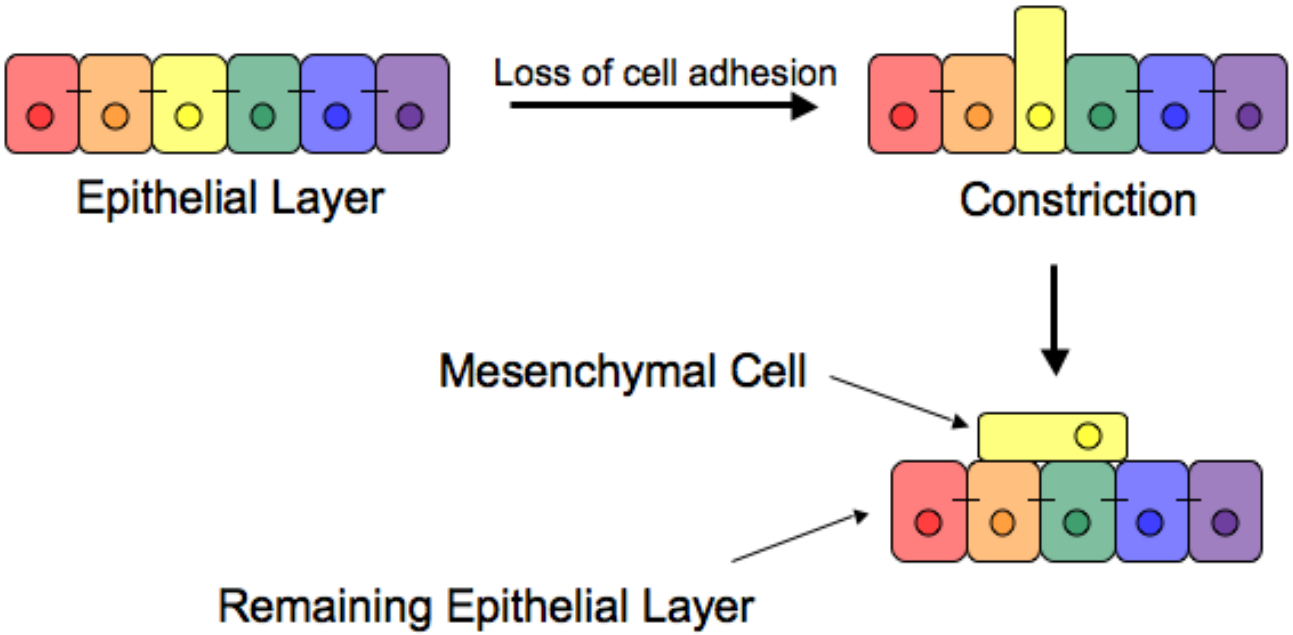
5. Potential mechanism

* Most researchers view:
* Epithelial–mesenchymal transition (EMT)
* A process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties to become mesenchymal stem cells.

Results & Discussion

5. Potential mechanism

* Epithelial–mesenchymal transition (EMT)



From: wikipedia

Results & Discussion

5. Potential mechanism

* Epithelial–mesenchymal transition (EMT)
* EMT is essential for numerous developmental processes including mesoderm formation and neural tube formation.
* EMT has also been shown to occur in wound healing, in organ fibrosis and in the **initiation of metastasis for cancer progression**.

From: wikipedia

Results & Discussion

5. Potential mechanism

* Negative expression of Cav-1

* Epithelial–mesenchymal transition (EMT)

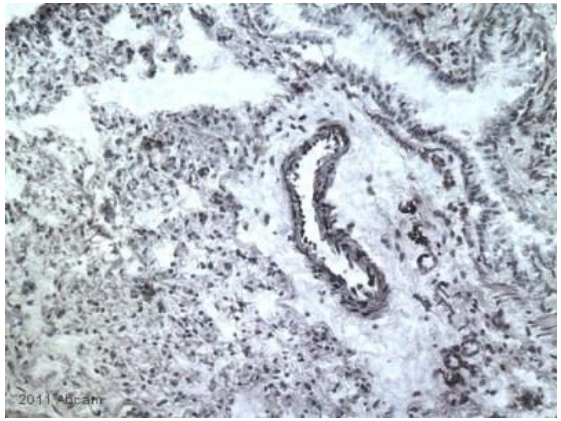
* Initiation and completion of the invasion-metastasis cascade

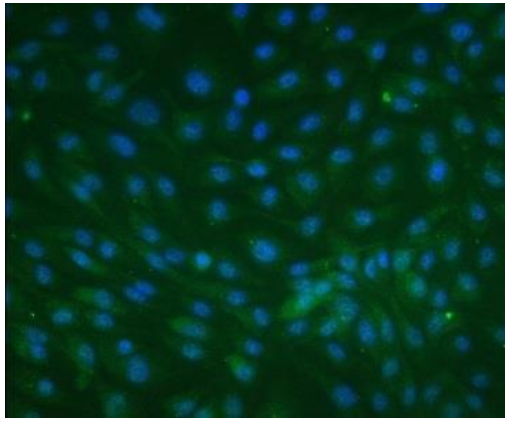
* Poor prognosis of breast cancer

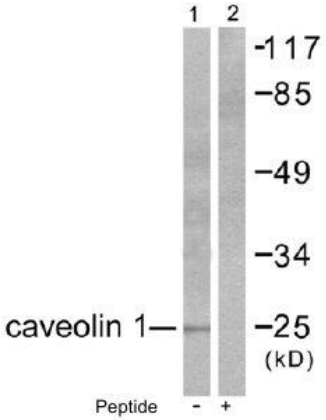
Results & Discussion

6. Application:

* Immunohistochemistry, Immunofluorescence, Western blot







Results & Discussion

7. Limitations

* Multivariate survival analysis **VS** univariate
* DFS and PFS together as DFS/PFS group
* Publication bias
* Definition of low & high expression of Cav

Results & Discussion

8. Future research:

* 1. The underlying mechanism.
* 2. Quantification and cut-off value in the detection of caveolin.

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* **Conclusion**

Conclusion

* Our results indicated that **negative expression of stromal Cav-1** was associated with **poor prognosis** of breast cancer, while the detection of Cav-1 and Cav-2 in tumor epithelial cells was not.
* However, these results should be confirmed by adequately multi-center designed prospective studies in the future.

Thanks for your attention!

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