High Expression of MTA1 Predicts Unfavorable Survival in Patients With Oral Squamous Cell Carcinoma

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Abstract. *Background/Aim: Metastasis-associated protein 1 (MTA1) plays a role in ATP-dependent nucleosome disruption activity and histone deacetylase activity and may indicate DNA methylation activity. MTA1 may also be involved in the progression of oral squamous cell carcinoma (OSCC). Patients and Methods: MTA1 immunoreactivity was analyzed using immunohistochemical (IHC) staining analysis in specimens from 281 OSCC patients. Kaplan-Meier analysis was used to determine the prognostic value of MTA1 for overall survival. Results: High MTA1 expression was significantly associated with female gender and lymph node metastasis. Multivariate analyses showed the independent prognostic role of high MTA1 expression in patients with OSCC of poorer mean survival. Conclusion: MTA1 expression, detected by IHC staining, could be an independent prognostic marker for patients of OSCC.*

Accounting for approximately 4% of all cancer cases, oral cancer is the sixth most common cancer worldwide (1). It is more common in men and usually occurs after the fifth decade of life (2). Squamous cell carcinomas include 90% of all oral cancer cases (3). Despite recent advances in imaging,

surgical techniques, and adjuvant therapy and an improved understanding of the molecular mechanisms of pathogenesis, overall survival has shown only a 5% improvement in the last 20 years (4). A good prognosis for stage I/II patients is expected (5). However, for those diagnosed in advanced stages, survival is poor and the cure rate is unsatisfactory (6). Predicting the response to nonsurgical treatment using conventional TNM-system data is still insufficient, and additional studies on biomarkers are still needed (6).

Metastasis is an important hallmark of cancer (7). Of all the reasons leading to cancer deaths, metastasis has a significant effect (8). Typically, metastasis involves a process known as epithelial to mesenchymal transition (EMT). During EMT, the motility of cancer cells is increased and the possibility of developing an invasive phenotype is enhanced (9). Some potent inducers are involved in EMT progression, and the TGF- β -MTA1-SOX4-EZH2 signaling axis plays an important role (10). First identified in 1994 by Toh *et al.* using differential cDNA library screening, metastasis-associated protein 1 (MTA1) over-expression has been found to correlate with invasion and metastasis of breast cancer (11, 12). MTA1 is an essential component of nucleosome remodeling and deacetylase complex, which has ATP-dependent nucleosome disruption and histone deacetylase activities, and may provide DNA methylation activity (13, 14). Research has shown that MTA1 is over-expressed in a wide range of human cancers and plays an important role in tumor progression and metastasis (8, 15-19). However, studies of MTA1 expression in oral cancer are still limited.

In this study, we evaluated the clinical significance of MTA1 expression in patients with oral squamous cell carcinoma (OSCC). Using clinical samples, we examined whether high expression of MTA1 in OSCC tissues could predict the prognosis of OSCC patients.

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Figure 1. Representative immunostaining for MTA1 in oral squamous cell carcinoma specimens. The MTA1 expression levels were (A) low and (B) high.

Patients and Methods

Patients. In this study, 281 tumor samples from patients with OSCC were examined. The cancers were staged according to the *AJCC Cancer Staging Manual*. The clinicopathological features collected from the established database included risk factors, histological type, differentiation, and TNM stage. The histological diagnoses had previously been confirmed by two pathologists (20, 21). Those patients with missing data or tissue loss during the immunohistochemical (IHC) staining procedure were excluded from this study to reduce the bias from missing data. The study was approved by the Institutional Review Board and Ethics Committee of the Changhua Christian Hospital, Changhua, Taiwan (IRB No. 180713). All methods were carried out in accordance with relevant guidelines and regulations.

IHC staining for MTA1. The IHC staining was performed at the Department of Surgical Pathology of Changhua Christian Hospital using an anti-human-MTA1 antibody (Santa Cruz sc-17773; 1:50 dilution) as previously described (20, 22). The immunoreactivity scores were analyzed by the pathologists using a previously described scoring protocol (22, 23), and the pathologists were blind to the prognostic data of the study. A final consensus was obtained for each score by having all the evaluators view the specimens simultaneously through a multiheaded microscope (Olympus BX51 10-headed microscope). The immunoreactivity scores were defined as cell staining intensity (0-3) multiplied by the percentage of stained cells (0%-100%), leading to scores of 0 to 300 (20, 22).

Statistical analyses. The χ^2 test was applied for both continuous and discrete data analysis. The associations between MTA1 expression and overall patient survival were estimated using univariate analysis and the Kaplan-Meier method and assessed further using the log-rank test (23, 24). Cox regression models of univariate and multivariate analysis were used to account for hazard ratio (HR) without or with adjustment of potential confounders, with MTA1 expression fitted as an indicator variable. In Cox regression analysis, statistical significance was presented with 95% confidence interval (95%CI) and *p*-value. All the statistical analyses were conducted using SPSS statistical software (version 15.0; SPSS Inc., Chicago, IL, USA). All the statistical tests were two-sided, and values of *p*<0.05 were considered statistically significant.

Table I. Relationships between MTA1 expression and clinical parameters in OSCC patients.

Parameters	Case number	MTA1 expression		<i>p</i> -Value
		Low	High	
Age (years)		55.9±10.4	57.0±12.6	0.417
Gender				
Female	45	15 (33.3)	30 (66.7)	0.002
Male	236	138 (58.5)	98 (41.5)	
Smoking				
No	164	82 (50.0)	82 (50.0)	0.076
Yes	117	71 (60.7)	46 (39.3)	
Betel quid chewing				
No	226	120 (53.1)	106 (46.9)	0.357
Yes	55	33 (60.0)	22 (40.0)	
Differentiation				
Well	43	27 (62.8)	16 (37.2)	0.233
Moderate+Poor	238	126 (52.9)	112 (47.1)	
Stage				
I	55	30 (54.5)	25 (45.5)	0.987
II+III+IV	226	123 (54.4)	103 (45.6)	
T value				
1+2+3	180	97 (53.9)	83 (46.1)	0.801
4	101	56 (55.4)	45 (44.6)	
N value				
0	173	108 (62.4)	65 (37.6)	0.001
1+2+3	108	45 (41.7)	63 (58.3)	

Results

Relationship between MTA1 expression and clinical parameters in patients with OSCC. The expression of MTA1 was investigated by IHC using primary tumor tissues from 281 OSCC patients (Figure 1). Table I shows the relationship between MTA1 expression and clinical parameters. Among the 281 patients with OSCC, high MTA1 protein expression was present in 128. MTA1 expression was not significantly

Table II. Univariate analysis of the influence of various parameters on the overall survival of OSCC patients.

Parameter	Category	Overall survival			p-Value
		Mean survival (yrs)	HR	95%CI	
Age	≥57/<57	6.2/5.9	0.935	0.652-1.341	0.716
Gender	Male/Female	6.0/6.3	1.283	0.747-2.204	0.367
Smoking	Yes/No	6.3/5.7	0.828	0.574-1.195	0.313
Betel quid chewing	Yes/No	6.5/5.9	0.806	0.498-1.303	0.378
Stage	II+III+IV/I	5.7/7.3	1.997	1.162-3.432	0.012
MTA1	High/Low	5.4/6.5	1.501	1.049-2.148	0.026

associated with age, smoking, betel quid chewing, differentiation, stage, or T value. However, we found that gender ($p=0.002$) and lymph node metastasis (N value) ($p=0.001$) exhibited a significant correlation with MTA1 expression. High MTA1 expression was observed in 66.7% (30/45) of female patients and 41.5% (98/236) of male patients. The high expression rates of MTA1 in patients with and without lymph node metastasis were 58.3% (63/108) and 37.6% (65/173), respectively.

MTA1 is an independent factor associated with OSCC overall survival. We performed univariate analyses of various parameters, and the selected explanatory variables were age, gender, smoking, betel quid chewing, stage, and MTA1 expression. The mean survival for stage II-IV patients and stage I patients was 5.7 years and 7.3 years, respectively (HR=1.997, 95% CI=1.162-3.432, $p=0.012$; Table II). High and low expression levels of MTA1 were associated with an even worse mean survival of 5.4 years and 6.5 years, respectively (HR=1.501, 95%CI=1.049-2.148, $p=0.026$, Table II). Patients with high MTA1 expression exhibited significantly poorer overall survival than patients with low MTA1 expression, as shown by Kaplan-Meier analysis (Figure 2). Multivariate analysis was used to clarify the independent prognostic role of MTA1 expression in patients with OSCC. After adjusting for age, gender, smoking, betel chewing, and stage, advanced-stage patients showed poor prognosis (HR=1.997, 95%CI=1.162-3.432, $p=0.012$, Table III). MTA1 expression remained statistically significant regarding its effect on the overall survival of patients with OSCC (HR=1.526, 95%CI=1.062-2.191, $p=0.022$; Table III).

Discussion

To the best of our knowledge, this study is the first to evaluate the association between MTA1 expression and overall survival of OSCC patients. In the present study, MTA1 protein levels in patient samples were determined using IHC analysis. Of all the clinical parameters investigated, only gender and lymph node metastasis were

Figure 2. Kaplan-Meier survival of oral squamous cell carcinoma patients according to MTA1 expression.

found to be remarkably correlated with MTA1 expression. The mean survival years of non-advanced-stage patients and patients with low MTA1 expression were significantly longer than those of advanced-stage patients and patients with high MTA1 expression. These results suggest that MTA1 expression in OSCC tissues may be a feasible biomarker for patient prognosis.

Kawasaki *et al.* analyzed the expression of MTA1 in 38 patients with OSCC. They found that the levels of MTA1 were significantly associated with cancer cell invasion and lymph node metastasis. In an analysis of 44 OSCC patients, high expression of MTA1 was revealed to be closely correlated with tumor progression and increased tumor angiogenesis (25). Our findings are consistent with those of previous studies of the association between MTA1 expression and lymph node metastasis in OSCC patients (25, 26). Furthermore, we evaluated overall survival, which showed poorer prognosis of patients with high levels of MTA1. In other studies, MTA1

Table III. Multivariate analysis of the influence of various parameters on the overall survival of OSCC patients.

Parameters	Category	Overall survival			
		Mean survival (yrs)	HR*	95%CI*	p-Value
Age	≥57/<57	6.2/5.9	0.881	0.607-1.279	0.505
Gender	Male/Female	6.0/6.3	1.393	0.786-2.468	0.256
Smoking	Yes/No	6.3/5.7	0.770	0.495-1.200	0.248
Betel quid chewing	Yes/No	6.5/5.9	0.825	0.464-1.465	0.511
Stage	II+III+IV/I	5.7/7.3	2.068	1.188-3.601	0.010
MTA1	High/Low	5.4/6.5	1.526	1.062-2.191	0.022

*Adjusted for age, gender, smoking, betel quid chewing, and stage.

was over-expressed in highly metastatic cells in various cancers (18, 27, 28). Thus, elevated MTA1 levels appear to be correlated with unfavorable survival outcomes.

However, we found a significant correlation between gender and MTA1 expression, which contrasted with the findings of previous studies (29, 30). We hypothesized that this could be associated with the expression of the estrogen receptor subtype alpha (ERα). ERα plays an important role in the regulation of cell growth (31) and has been found to promote tumorigenesis and to be a therapeutic target in some cancers (32-35). Some studies have found a correlation between the expression of ERα and MTA1. Mao *et al.* found that MTA1 expression correlates with ERα methylation, which was linked to the lack of ERα expression in breast cancer, and that a demethylating agent could down-regulate MTA1 expression (36, 37). A study indicated that inhibition of MTA1 transcription by ERα suppresses the proliferation and invasion of human hepatocellular carcinoma cells (38). Zhao *et al.* found that tumors with high MTA1 expression were ER negative significantly more often compared to tumors with low expression and had shorter disease-free survival than androgen receptor positive/estrogen receptor positive tumors. ERα could also be found in OSCC (31). In a previous study, ERα expression was analyzed in OSCC patients and was found to be present only in older male patients (39). This may support our finding that MTA1 expression is higher in females, which may due to the silence of ERα.

The present study evaluated the association between MTA1 expression and overall survival of OSCC patients. In line with previous studies, this study indicated that MTA1 was a prognostic factor of OSCC patients. However, we found that high expression of MTA1 was present significantly more often in female rather in male patients, which contrasted with the results of previous studies. This may be caused by the difference in population or other mechanisms. We hypothesized that ERα influences MTA1 transcription and expression in OSCC patients, but the interaction between MTA1 and ERα was unclear. Further investigations of these mechanisms are needed.

Evaluation of the association between MTA1 expression and overall survival of OSCC patients using IHC staining indicated that MTA1 has the potential to be a prognostic factor. In contrast to other studies, MTA1 expression showed a significant difference between the two genders, with an unknown cause.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

Conception and design: Sung WW; acquisition of data: Yeh CM, Chao WR; analysis and interpretation of data: Lin KY, Su TC; drafting of the manuscript: Lin KY; critical revision of the manuscript: Su TC; statistical analysis: Lin KY, Su TC, Sung WW; supervision: Sung WW.

References

- Omura K: Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma. *Int J Clin Oncol* 19(3): 423-430, 2014. PMID: 24682763. DOI: 10.1007/s10147-014-0689-z
- Montero PH and Patel SG: Cancer of the oral cavity. *Surg Oncol Clin N Am* 24(3): 491-508, 2015. PMID: 25979396. DOI: 10.1016/j.soc.2015.03.006
- Lingen MW, Kalmar JR, Karrison T and Speight PM: Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncol* 44(1): 10-22, 2008. PMID: 17825602. DOI: 10.1016/j.oraloncology.2007.06.011
- Chinn SB and Myers JN: Oral cavity carcinoma: current management, controversies, and future directions. *J Clin Oncol* 33(29): 3269-3276, 2015. PMID: 26351335. DOI: 10.1200/JCO.2015.61.2929
- Güneri P and Epstein JB: Late stage diagnosis of oral cancer: components and possible solutions. *Oral Oncol* 50(12): 1131-1136, 2014. PMID: 25255960. DOI: 10.1016/j.oraloncology.2014.09.005
- Rivera C: Essentials of oral cancer. *Int J Clin Exp Pathol* 8(9): 11884-11894, 2015. PMID: 26617944.

- 7 Hanahan D and Weinberg RA: Hallmarks of cancer: the next generation. *Cell* 144(5): 646-674, 2011. PMID: 21376230. DOI: 10.1016/j.cell.2011.02.013
- 8 Malisetty VL, Penugurti V, Panta P, Chitta SK and Manavathi B: MTA1 expression in human cancers - Clinical and pharmacological significance. *Biomed Pharmacother* 95: 956-964, 2017. PMID: 28915537. DOI: 10.1016/j.biopha.2017.09.025
- 9 Lamouille S, Xu J and Derynck R: Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol* 15(3): 178-196, 2014. PMID: 24556840. DOI: 10.1038/nrm3758
- 10 Li L, Liu J, Xue H, Li C, Liu Q, Zhou Y, Wang T, Wang H, Qian H and Wen T: A TGF- β -MTA1-SOX4-EZH2 signaling axis drives epithelial-mesenchymal transition in tumor metastasis. *Oncogene* 39(10): 2125-2139, 2020. PMID: 31811272. DOI: 10.1038/s41388-019-1132-8
- 11 Toh Y, Pencil SD and Nicolson GL: A novel candidate metastasis-associated gene, mta1, differentially expressed in highly metastatic mammary adenocarcinoma cell lines. cDNA cloning, expression, and protein analyses. *J Biol Chem* 269(37): 22958-22963, 1994. PMID: 8083195.
- 12 Toh Y, Pencil SD and Nicolson GL: Analysis of the complete sequence of the novel metastasis-associated candidate gene, mta1, differentially expressed in mammary adenocarcinoma and breast cancer cell lines. *Gene* 159(1): 97-104, 1995. PMID: 7607577. DOI: 10.1016/0378-1119(94)00410-t
- 13 Xue Y, Wong J, Moreno GT, Young MK, Côté J and Wang W: NURD, a novel complex with both ATP-dependent chromatin-remodeling and histone deacetylase activities. *Mol Cell* 2(6): 851-861, 1998. PMID: 9885572. DOI: 10.1016/s1097-2765(00)80299-3
- 14 Zhang Y, Ng HH, Erdjument-Bromage H, Tempst P, Bird A and Reinberg D: Analysis of the NuRD subunits reveals a histone deacetylase core complex and a connection with DNA methylation. *Genes Dev* 13(15): 1924-1935, 1999. PMID: 10444591. DOI: 10.1101/gad.13.15.1924
- 15 Ryu SH, Chung YH, Lee H, Kim JA, Shin HD, Min HJ, Seo DD, Jang MK, Yu E and Kim KW: Metastatic tumor antigen 1 is closely associated with frequent postoperative recurrence and poor survival in patients with hepatocellular carcinoma. *Hepatology* 47(3): 929-936, 2008. PMID: 18306220. DOI: 10.1002/hep.22124
- 16 Sun X, Zhang Y, Li B and Yang H: MTA1 promotes the invasion and migration of pancreatic cancer cells potentially through the HIF- α /VEGF pathway. *J Recept Signal Transduct Res* 38(4): 352-358, 2018. PMID: 30396299. DOI: 10.1080/10799893.2018.1531887
- 17 Chen WH, Cai MY, Zhang JX, Wang FW, Tang LQ, Liao YJ, Jin XH, Wang CY, Guo L, Jiang YG, Ren CP, Mai HQ, Zeng MS, Kung HF, Qian CN and Xie D: FMNL1 mediates nasopharyngeal carcinoma cell aggressiveness by epigenetically upregulating MTA1. *Oncogene* 37(48): 6243-6258, 2018. PMID: 30013189. DOI: 10.1038/s41388-018-0351-8
- 18 Zhou N, Wang H, Liu H, Xue H, Lin F, Meng X, Liang A, Zhao Z, Liu Y and Qian H: MTA1-upregulated EpCAM is associated with metastatic behaviors and poor prognosis in lung cancer. *J Exp Clin Cancer Res* 34: 157, 2015. PMID: 26698569. DOI: 10.1186/s13046-015-0263-1
- 19 Zeng H, Zhang JM, Du Y, Wang J, Ren Y, Li M, Li H, Cai Z, Chu Q and Yang C: Crosstalk between ATF4 and MTA1/HDAC1 promotes osteosarcoma progression. *Oncotarget* 7(6): 7329-7342, 2016. PMID: 26797758. DOI: 10.18632/oncotarget.6940
- 20 Hwang JC, Sung WW, Tu HP, Hsieh KC, Yeh CM, Chen CJ, Tai HC, Hsu CT, Shieh GS, Chang JG, Yeh KT and Liu TC: The overexpression of FEN1 and RAD54B may act as independent prognostic factors of lung adenocarcinoma. *PLoS One* 10(10): e0139435, 2015. PMID: 26431531. DOI: 10.1371/journal.pone.0139435
- 21 Lee YJ, Chan L, Yeh CM, Lee CH and Sung WW: Overexpression of KLF17 predicts a favorable prognosis in patients with oral squamous cell carcinoma: a retrospective study. *Medicina (Kaunas)* 56(2): 57, 2020. PMID: 32019121. DOI: 10.3390/medicina56020057
- 22 Sung WW, Lin YM, Wu PR, Yen HH, Lai HW, Su TC, Huang RH, Wen CK, Chen CY, Chen CJ and Yeh KT: High nuclear/cytoplasmic ratio of Cdk1 expression predicts poor prognosis in colorectal cancer patients. *BMC Cancer* 14: 951, 2014. PMID: 25511643. DOI: 10.1186/1471-2407-14-951
- 23 Sung WW, Wang YC, Cheng YW, Lee MC, Yeh KT, Wang L, Wang J, Chen CY and Lee H: A polymorphic -844T/C in FasL promoter predicts survival and relapse in non-small cell lung cancer. *Clin Cancer Res* 17(18): 5991-5999, 2011. PMID: 21807637. DOI: 10.1158/1078-0432.CCR-11-0227
- 24 Sung WW, Wang YC, Lin PL, Cheng YW, Chen CY, Wu TC and Lee H: IL-10 promotes tumor aggressiveness via upregulation of CIP2A transcription in lung adenocarcinoma. *Clin Cancer Res* 19(15): 4092-4103, 2013. PMID: 23743567. DOI: 10.1158/1078-0432.CCR-12-3439
- 25 Andishehtadbir A, Najvani AD, Pardis S, Ashkavandi ZJ, Ashraf MJ, Khademi B and Kamali F: Metastasis-associated protein 1 expression in oral squamous cell carcinomas: correlation with metastasis and angiogenesis. *Turk Patoloji Derg* 31(1): 9-15, 2015. PMID: 25301048. DOI: 10.5146/tjpath.2014.01277
- 26 Kawasaki G, Yanamoto S, Yoshitomi I, Yamada S and Mizuno A: Overexpression of metastasis-associated MTA1 in oral squamous cell carcinomas: correlation with metastasis and invasion. *Int J Oral Maxillofac Surg* 37(11): 1039-1046, 2008. PMID: 18640824. DOI: 10.1016/j.ijom.2008.05.020
- 27 Yuan T, Zhang H, Liu B, Zhang Q, Liang Y, Zheng R, Deng J and Zhang X: Expression of MTA1 in nasopharyngeal carcinoma and its correlation with prognosis. *Med Oncol* 31(12): 330, 2014. PMID: 25416046. DOI: 10.1007/s12032-014-0330-z
- 28 Lv ZY, Zhao ZS, Ye ZY, Wang YY, Wang HJ and Yang Q: Metastasis-associated protein 1 (MTA1) in gastric cancer tissues is positively associated with poorer prognosis. *Pathol Res Pract* 214(4): 536-541, 2018. PMID: 29573865. DOI: 10.1016/j.prp.2018.02.011
- 29 Zhu X, Guo Y, Li X, Ding Y and Chen L: Metastasis-associated protein 1 nuclear expression is associated with tumor progression and clinical outcome in patients with non-small cell lung cancer. *J Thorac Oncol* 5(8): 1159-1166, 2010. PMID: 20661085. DOI: 10.1097/JTO.0b013e3181e04d98
- 30 Yu CH, Chen HH, Wang JT, Liu BY, Wang YP, Sun A, Kuo RC and Chiang CP: Nuclear expression of metastasis-associated protein 1 (MTA1) is inversely related to progression of oral squamous cell carcinoma in taiwan. *J Dent Sci* 2(1): 1-10, 2007. DOI: 10.30086/jds.200703.0001
- 31 Chang YL, Hsu YK, Wu TF, Huang CM, Liou LY, Chiu YW, Hsiao YH, Luo FJ and Yuan TC: Regulation of estrogen receptor α function in oral squamous cell carcinoma cells by FAK

- signaling. *Endocr Relat Cancer* 21(4): 555-565, 2014. PMID: 24825747. DOI: 10.1530/ERC-14-0102
- 32 Yip CH and Rhodes A: Estrogen and progesterone receptors in breast cancer. *Future Oncol* 10(14): 2293-2301, 2014. PMID: 25471040. DOI: 10.2217/fon.14.110
- 33 Andersen CL, Sikora MJ, Boisen MM, Ma T, Christie A, Tseng G, Park Y, Luthra S, Chandran U, Haluska P, Mantia-Smaldone GM, Odunsi K, McLean K, Lee AV, Elishaev E, Edwards RP and Oesterreich S: Active estrogen receptor- α signaling in ovarian cancer models and clinical specimens. *Clin Cancer Res* 23(14): 3802-3812, 2017. PMID: 28073843. DOI: 10.1158/1078-0432.CCR-16-1501
- 34 Liu S, Fan W, Gao X, Huang K, Ding C, Ma G, Yan L and Song S: Estrogen receptor α regulates the Wnt/ β -catenin signaling pathway in colon cancer by targeting the NOD-like receptors. *Cell Signal* 61: 86-92, 2019. PMID: 31121307. DOI: 10.1016/j.cellsig.2019.05.009
- 35 Bonkhoff H: Estrogen receptor signaling in prostate cancer: Implications for carcinogenesis and tumor progression. *Prostate* 78(1): 2-10, 2018. PMID: 29094395. DOI: 10.1002/pros.23446
- 36 Mao XY, Chen H, Wang H, Wei J, Liu C, Zheng HC, Yao F and Jin F: MTA1 expression correlates significantly with ER- α methylation in breast cancer. *Tumour Biol* 33(5): 1565-1572, 2012. PMID: 22644675. DOI: 10.1007/s13277-012-0410-7
- 37 Flanagan JM, Cocciardi S, Waddell N, Johnstone CN, Marsh A, Henderson S, Simpson P, da Silva L, kConFab Investigators., Khanna K, Lakhani S, Boshoff C and Chenevix-Trench G: DNA methylome of familial breast cancer identifies distinct profiles defined by mutation status. *Am J Hum Genet* 86(3): 420-433, 2010. PMID: 20206335. DOI: 10.1016/j.ajhg.2010.02.008
- 38 Deng L, Yang H, Tang J, Lin Z, Yin A, Gao Y, Wang X, Jiang R and Sun B: Inhibition of MTA1 by ER α contributes to protection hepatocellular carcinoma from tumor proliferation and metastasis. *J Exp Clin Cancer Res* 34: 128, 2015. PMID: 26503703. DOI: 10.1186/s13046-015-0248-0
- 39 Grimm M, Biegner T, Teriete P, Hoefert S, Krimmel M, Munz A and Reinert S: Estrogen and Progesterone hormone receptor expression in oral cavity cancer. *Med Oral Patol Oral Cir Bucal* 21(5): e554-e558, 2016. PMID: 27475696. DOI: 10.4317/medoral.21182

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