

CD24 overexpression in cancer development and progression: A meta-analysis

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Abstract. CD24 has emerged as a new oncogene and metastasis promoter. However, there is a controversy as to whether CD24 expression is a prognostic factor for poor outcomes in many human cancers. To shed light on this controversy, we performed a meta-analysis of the relationship between CD24 expression and prognostic parameters in different carcinomas. Studies published in the period 1990-2009 were reviewed for the meta-analysis and selected according to defined criteria. The effect sizes of prognostic parameters and overall survival were calculated by an odds ratio (OR) or an adjusted hazard ratio (HR). Twenty-eight studies reported CD24 expression for 2,925 cases. The frequency of CD24 expression by immunohistochemistry was 68% in all the carcinomas of the breast, female genital tract, gastrointestinal tract, biliary tract and pancreas, urinary system, prostate and skin. Overall, CD24 was more frequently overexpressed in their carcinomas than their benign lesions (OR=4.21; 95% CI, 1.826-9.731; P=0.001) and was significantly associated with lymph node metastasis (OR=2.41; CI, 1.013-5.720; P=0.047), advanced clinical stages (OR=1.59; 95% CI, 1.244-2.032; P<0.001) and shortened overall survival (HR=2.13; 95% CI, 1.656-2.730; P<0.001). CD24 expression was highly associated with lymph node metastases in breast cancer (OR=3.55; 95% CI, 1.664-7.554; P=0.001), advanced clinical stages (OR=2.22; 95% CI, 1.442-3.418; P<0.001) and lymphovascular invasions (OR=2.78; 95% CI, 1.522-5.068; P=0.001) in urothelial carcinomas and with higher grades in endometrial adenocarcinomas (OR=3.88; 95% CI, 1.548-9.715; P=0.004). CD24 was more frequently and strongly expressed in breast (OR=35.80; 95% CI, 8.907-143.921; P<0.001) and ovarian carcinomas (OR=35.92; CI, 7.156-180.311; P<0.001), than in their benign counterparts. In conclusion, the meta-analysis strongly supports the idea that CD24 is an important marker of malignancy and poor prognosis in various cancers. In particular, CD24 may promote cancer development and progression in the breast, ovary and urinary bladder.

Introduction

Accumulating evidence indicates that CD24 expression is an important biomarker for diagnosis and progression in many carcinomas (1-3). CD24 is a small 27 amino acid glycoprotein at the outer surface of the cell membrane and is attached to the cell membrane by a glycosylphosphatidyl-inositol (GPI) anchor (1,2). In human tissues, CD24 protein was first reported to be expressed by pre-B lymphocytes, but it is lost during maturation to plasma cells (4). This protein had been recognized only as a cell marker for hematopoietic cell lineages.

In recent years, many studies have described CD24 expression in carcinomas arising in various organs using immunohistochemistry (5-32). Most studies reported that overexpression of CD24 protein or CD24 positivity is significantly associated with malignant transformation or poor clinicopathologic parameters in a variety of carcinomas, especially breast cancer (1-3,5-9,11-28,30,31). In contrast, several studies have suggested that the absence or low expression of CD24 might be related to tumor growth, invasiveness or metastasis in breast cancer (33-36). In addition, it has been reported that the clinicopathologic significance of CD24 is different even among the studies using the same type of carcinomas arising in the same organ (5-24). In an attempt to address these controversies, we performed a meta-analysis to examine the relationship between CD24 expression and clinicopathologic parameters.

Materials and methods

Eligibility criteria for meta-analysis. We extensively searched for studies that examined associations between CD24 expression and clinicopathological characteristics related to various carcinomas. The following type of articles were included: i) Articles demonstrating that CD24 is expressed in primary cancer tissue as indicated by immunohistochemistry; articles that dealt with cell lines or animals were excluded; ii) Articles published in English before February 2009; iii) the most informative article when multiple articles were published by the same authors or groups. The following articles were excluded: i) review articles without original data; ii) articles lacking or containing inappropriately presented data; and iii) case studies.

Collection of published studies. An extensive search for publications was carried out using the PubMed database

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Table I. Characteristics of individual studies included in the meta-analysis.

Study	Patient's country	Location	No. of cases	CD24 + No. (%)	Comments
Fogel <i>et al</i> (5)	Israel	Breast	31	31 (100%)	Cancer > benign
Kristiansen <i>et al</i> (6)	Germany	Breast	201	170 (85%)	Lymph node metastasis, poor survival rate
Surowiak <i>et al</i> (7)	Poland	Breast	60	46 (77%)	Poor survival rate
Bircan <i>et al</i> (8)	Turkey	Breast	59	55 (93%)	Cancer > benign, grade
Lim <i>et al</i> (9)	Korea	Breast	22	22 (100%)	Cancer > benign
		Ovary	14	14 (100%)	Grade
		Gallbladder	14	12 (86%)	Cancer > benign
		Colon	31	30 (97%)	Cancer > benign, lymph node metastasis (C)
		Stomach	48	43 (90%)	Lymph node metastasis in AGC
Honeth <i>et al</i> (10)	Sweden	Breast	240	110 (46%)	NA
Athanassiadou <i>et al</i> (11)	Greece	Breast	70	54 (77%)	Grade, size, lymph node metastasis, stage
Kristiansen <i>et al</i> (12)	Germany	Ovary	56	51 (91%)	Poor survival rate (C)
Choi <i>et al</i> (13)	Korea	Ovary	71	71 (100%)	Poor survival rate (C)
Surowiak <i>et al</i> (14)	Poland	Ovary	43	34 (79%)	Poor survival rate
Santin <i>et al</i> (15)	USA	Ovary	10	10 (100%)	NA
Winkler <i>et al</i> (16)	Austria	Urinary tract	259	161 (62%)	Grade, angio-invasion, stage
Choi <i>et al</i> (17)	Korea	Bladder	135	83 (61%)	Grade, stage
Karahan <i>et al</i> (18)	Turkey	Endometrium	44	34 (77%)	Grade, lymph node metastasis, stage
Kim <i>et al</i> (19)	Korea	Endometrium	82	53 (64%)	Grade
Su <i>et al</i> (20)	Taiwan	Biliary tract	70	36 (51%)	Poor survival rate
Baumhoer <i>et al</i> (21)	Switzerland	Ampulla of Vater	152	83 (55%)	Cancer > benign
Sagiv <i>et al</i> (22)	Israel	Colorectal	66	57 (86%)	Cancer > normal
Weichert <i>et al</i> (23)	Germany	Colorectal	147	124 (84%)	Grade, lymph node metastasis, stage, poor survival rate (C)
Chou <i>et al</i> (24)	Taiwan	Stomach	103	63 (61%)	Stage, lymphovascular invasion, poor survival rate (C)
Kristiansen <i>et al</i> (25)	Germany	Lung	89	68 (76%)	Poor survival rate
Kristiansen <i>et al</i> (26)	Germany	Prostate	102	49 (48%)	Stage, poor survival rate
Sano <i>et al</i> (27)	Japan	Esophagus	151	61 (40%)	Lymph node metastasis, stage, poor survival rate
Lee <i>et al</i> (28)	Korea	Kidney	328	201 (61%)	Grade, size, poor progression free survival rate
Droz <i>et al</i> (29)	France	Kidney	28	28 (100%)	NA
Kwon <i>et al</i> (30)	Korea	Uterine cervix	73	43 (59%)	Poor distant metastasis free survival rate
Jacob <i>et al</i> (31)	Germany	Pancreas	95	68 (72%)	Grade
Deichmann <i>et al</i> (32)	Germany	Skin	31	29 (94%)	NA
Total			2925	1994 (68%)	

No., number; +, positive (membranous or cytoplasmic); cancer > benign, CD24 is increased in carcinoma compared to benign lesions; C, cytoplasmic expression; AGC, advanced gastric cancer; NA, not available; cancer > normal, CD24 is increased in carcinoma compared to normal.

(<http://www.ncbi.nlm.nih.gov/pubmed>). The keywords for our search consisted of 'CD24 + cancer' and 'CD24 + carcinoma', which retrieved 439 and 97 citations, respectively. We selected relevant studies on the basis of the summary analysis. We avoided obtaining duplicate data by carefully examining the authors' names and affiliations for each publication. Overlapping articles and articles unrelated to our analysis were excluded.

Data pooling and statistics. Meta-analysis was performed, as previously described (37). An effect size for each of the studies analyzed was estimated by an odds ratio (OR) using the Mantel-Haenszel method or a hazard ratio (HR). The choice to

use a random or fixed effect model for analysis depended on Q statistics. Statistical analysis was performed using Comprehensive Meta-analysis Software version 2.0 (Biostat, Englewood, NJ, USA); P-values <0.05 were considered statistically significant.

Results

Twenty-eight studies satisfied the selection criteria (5-32). The main features of the chosen studies are described in Table I. The selected studies included a total of 2,925 cases, and ranged from 10 to 328 patients. CD24 overexpression was found in 1,994 (68%) of the 2,925 patients. Ectopic

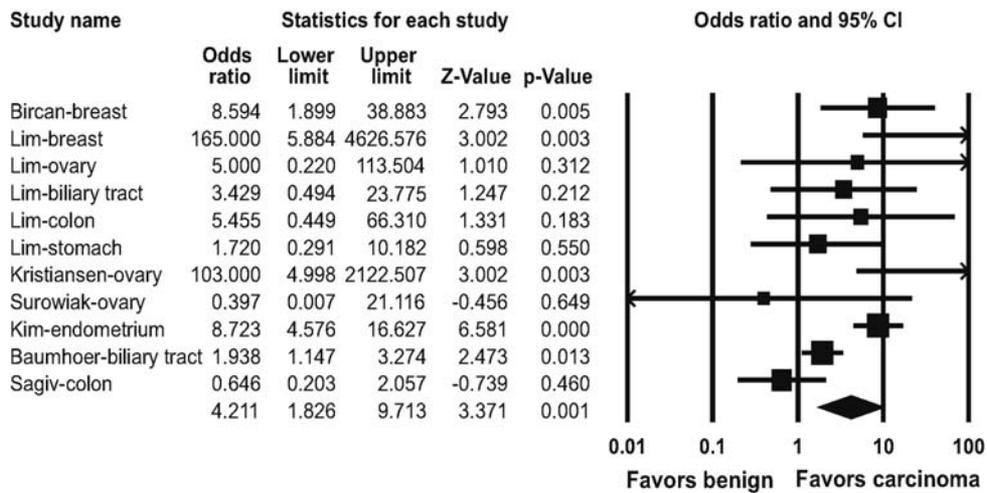


Figure 1. Odds ratios with corresponding 95% confidence intervals for individual studies and pooled data for the association of CD24 expression with benign lesions and carcinomas. The graph demonstrates effect sizes and 95% confidence intervals for each study and overall.

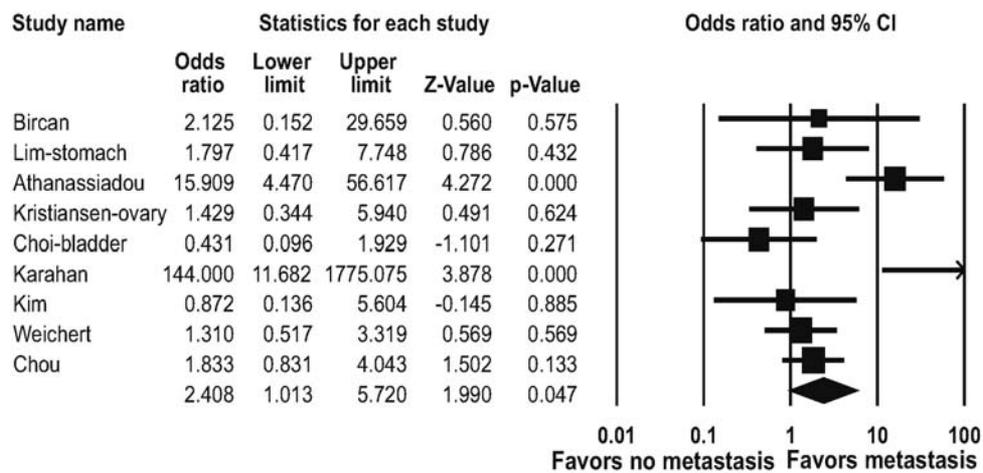


Figure 2. Pooled estimates of the association between cytoplasmic CD24 expression and lymph node metastasis.

expression of CD24 in the cytoplasm was observed in 805 (57%) of 1,409 patients. Seven studies presented CD24 comparisons between benign and malignant lesions (8,9,12,14,19,21,22). CD24 expression was detected in 432 (74%) of 587 carcinomas and in 158 (45%) of 351 benign lesions. There was significant statistical heterogeneity among the studies ($Q=33.924$, $df=10$, $P<0.001$). CD24 expression was upregulated more in carcinomas than in benign lesions (OR=4.211, 95% CI, 1.826-9.731; $P=0.001$) (Fig. 1).

Fifteen studies reported the relationship of CD24 expression to lymph node metastasis (6,8,9,11,18-20,23,25-28,30-32). CD24 expression was found in 376 (70%) of 538 cases with lymph node metastasis and in 522 (53%) of 994 cases without lymph node metastasis. Significant statistical heterogeneity was found among the studies ($Q=34.607$, $df=14$, $P=0.002$). CD24 expression was not associated with lymph node metastasis (OR=1.485, 95% CI, 0.909-2.426; $P=0.114$). However, nine studies reported the association of cytoplasmic staining of CD24 with lymph node metastasis (8,9,11,12,17-19,23,24). The cytoplasmic expression of

CD24 was found in 172 (70%) of 244 cases with lymph node metastasis and in 173 (51%) of 336 cases without lymph node metastasis. There was significant statistical heterogeneity among the studies ($Q=27.232$, $df=8$, $P=0.001$). CD24 expression in the cytoplasm was more associated with lymph node metastasis (OR=2.408, 95% CI, 1.013-5.720; $P=0.047$) (Fig. 2).

Thirteen studies investigated the relationship of CD24 expression to clinical stage (6,7,11,16,18,20,23,25-28,30,31). CD24 was detected in 318 (62%) of 511 cases with stages III or IV, whereas it was found in 654 (56%) of 1,170 cases with stages I or II. CD24 expression was associated with advanced clinical stages (OR=1.589, 95% CI, 1.244-2.032; $P<0.001$) (Fig. 3). Heterogeneity among the studies were not statistically significant ($Q=15.935$, $df=12$, $P=0.194$).

Eight studies including 1,133 patients reported exact HRs and CIs on overall survival adjusted for other prognostic factors according to total (membranous and/or cytoplasmic) or cytoplasmic CD24 expression (negative or low expression vs. positive or high expression) (6,12,13,23,25-28). The adjusted HRs that were estimated ranged from 1.54 to 5.37. The

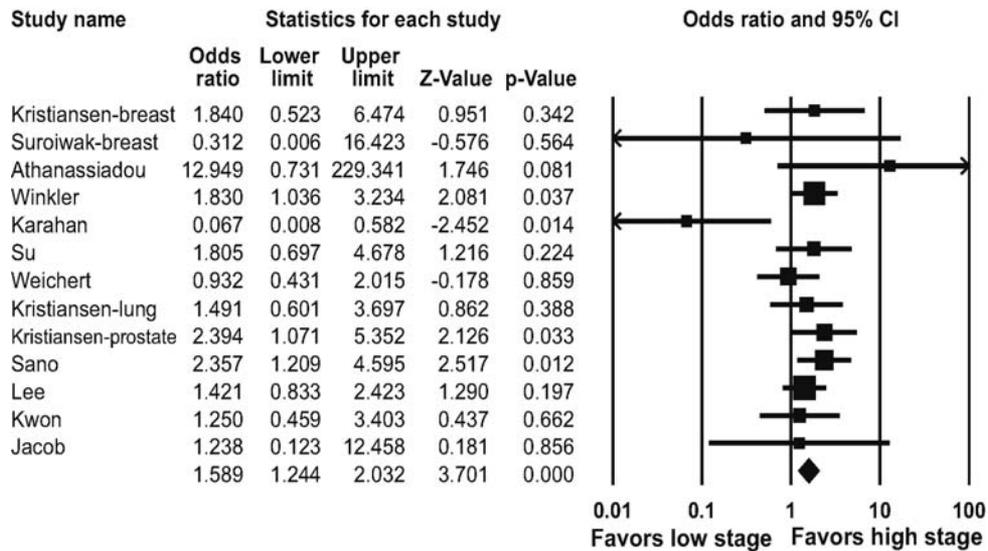


Figure 3. Pooled estimates of the association between CD24 expression and clinical stages.

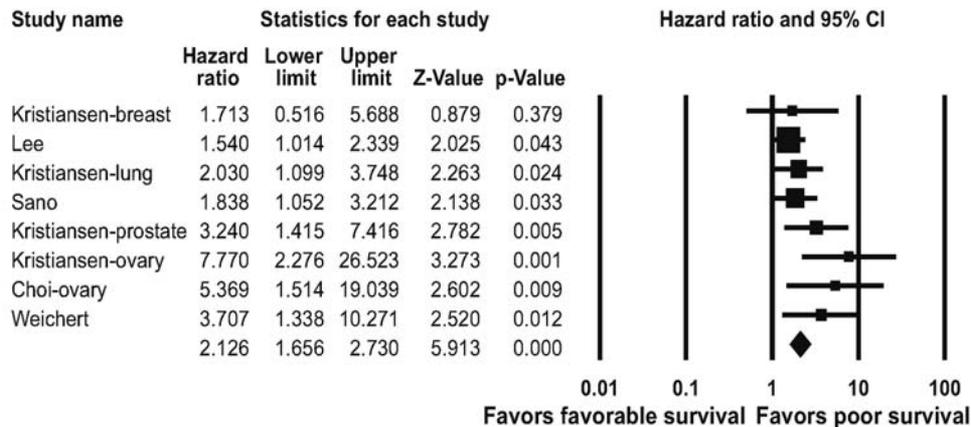


Figure 4. Hazard ratios with corresponding 95% confidence intervals of individual studies and pooled data for the association between CD24 expression and overall survival in a variety of carcinomas.

pooled HR for these studies was 2.126 (95% CI, 1.656-2.730; P<0.001) (Fig. 4). Heterogeneity among the studies were not statistically significant (Q=11.170, df=7, P=0.131).

Breast cancer. Seven studies presented CD24 expression in breast cancer patients (5-11). Out of 683 patients with breast cancer, CD24 expression was found in 488 (71%) patients while CD24 expression in the cytoplasm was observed in 422 (62%) cases. Three studies investigated cytoplasmic CD24 expression between benign and malignant lesions (5,8,9). Cytoplasmic staining of CD24 was found in 86 (78%) of 110 malignant lesions and in 2 (8%) of 25 benign lesions. CD24 expression in the cytoplasm was highly and significantly greater in carcinomas than in benign lesions (OR=35.803, 95% CI, 8.907-143.921; P<0.001) (Fig. 5). No significant heterogeneity was found among the studies (Q=4.235, df=2, P=0.120).

Three studies reported on the association of total CD24 expression with lymph node metastasis (6,8,11). CD24 expression was found in 151 (93%) of 162 cases with lymph node metastasis and in 92 (71%) of 130 cases without lymph

node metastasis. High expression of CD24 was significantly associated with lymph node metastasis (OR=3.546, 95% CI, 1.664-7.554; P=0.001) (Fig. 6). There was no significant heterogeneity in two studies (Q=5.113, df=2, P=0.078).

Three studies described CD24 expression according to tumor size (T3, 4 vs. T1, 2) (6,8,11), grade (3 vs. 1, 2) (6,8,11), clinical stage (III, IV vs. I, II) (6,7,11), or ER status and c-erbB2 expression (6,8). Tumor size (OR=1.347, 95% CI, 0.442-4.108; P=0.601), grade (OR=1.681, 95% CI, 0.730-3.870; P=0.222), clinical stage (OR=2.140, 95% CI, 0.708-6.471; P=0.178), ER status (OR=0.572, 95% CI, 0.233-1.405; P=0.223) and c-erbB2 (OR=2.213, 95% CI, 0.797-6.145; P=0.127) expression were not associated with CD24 expression.

Ovarian cancer. Five studies addressed membranous CD24 expression in ovarian cancer patients (9,12-15). Membranous CD24 expression was detected in 158 (81%) of 194 ovarian cancer patients. Four studies presented cytoplasmic CD24 expression among benign, borderline and malignant lesions (9,12-14). Cytoplasmic staining of CD24 was observed in

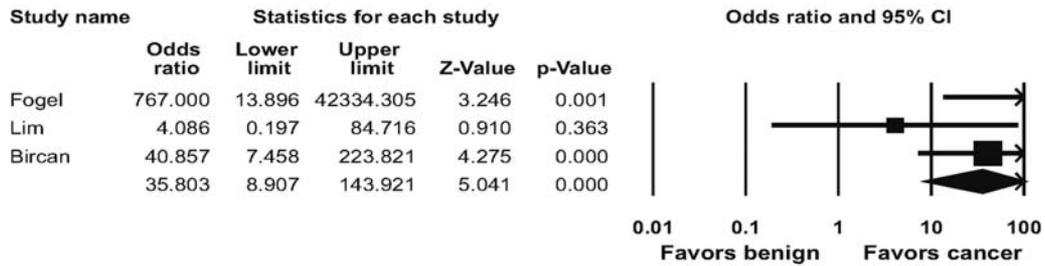


Figure 5. Pooled estimates of the association of cytoplasmic CD24 expression between benign lesions and carcinomas of the breast.

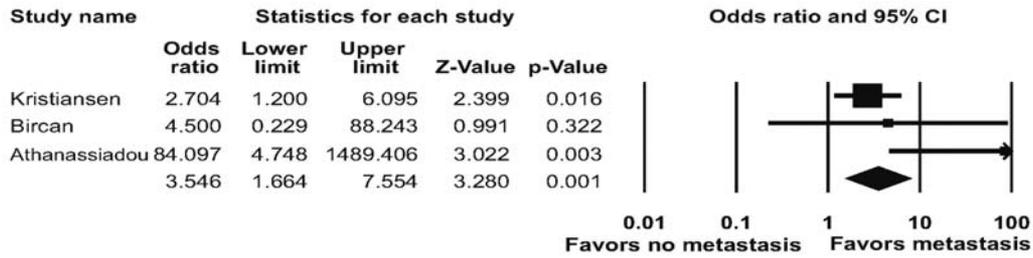


Figure 6. Pooled estimates of the association between CD24 expression and lymph node metastasis of breast cancer.

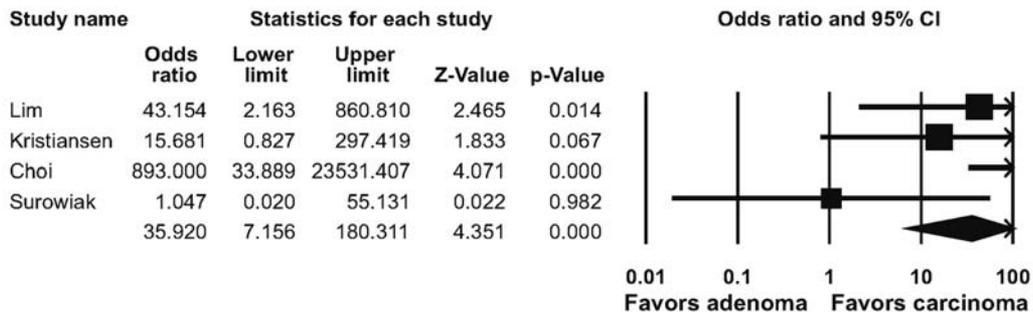


Figure 7. Pooled estimates of the association of cytoplasmic CD24 expression between adenomas and carcinomas in the ovary.

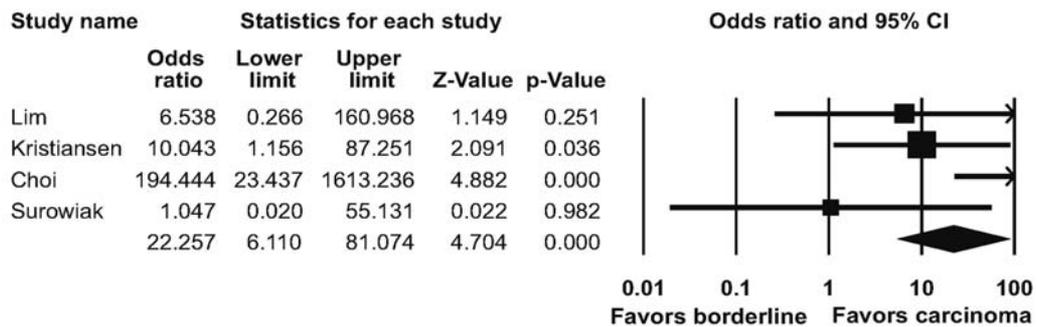


Figure 8. Pooled estimates of the association of cytoplasmic CD24 expression between borderline tumor and carcinoma in the ovary.

none (0%) of 30 adenomas, 10 (23%) of 44 borderline tumors and 133 (72%) of 184 ovarian carcinomas. Cytoplasmic CD24 expression was much greater in ovarian carcinoma patients than in patients with adenomas (OR=35.920, 95% CI, 7.156-180.311; P<0.001) (Fig. 7) and those with a borderline tumor (OR=22.257, 95% CI, 6.110-81.074; P<0.001) (Fig. 8).

There was no significant heterogeneity (Q=7.081, df=3, P=0.069, Q=7.398, df=3, P=0.060) among the studies, respectively. Two studies reported cytoplasmic expression of CD24 between tumor grades (3 vs. 1, 2) (12,14). Tumor grade (OR=1.607, 95% CI, 0.704-3.671; P=0.260) was not significantly associated with cytoplasmic CD24 expression.

Other clinicopathological parameters were not available for this meta-analysis.

Urothelial carcinoma. Two studies reported CD24 expression as a function of clinicopathologic parameters in urothelial carcinoma patients (16,17). CD24 overexpression was found in 244 (61.9%) of 394 urothelial carcinoma patients. CD24 overexpression was observed in 123 (72%) of 170 patients with higher stages (T2-4) and in 121 (54%) of 224 with lower stages (Ta, T1). High expression of CD24 was significantly associated with advanced clinical stages (OR=2.220, 95% CI, 1.442-3.418; P<0.001). No significant heterogeneity was found in two studies (Q=1.370, df=1, P=0.242).

CD24 expression was reported in 79 (81%) of 97 cases with lymphovascular invasion and in 104 (61%) of 170 cases without lymphovascular invasion. High expression of CD24 was significantly associated with lymphovascular invasion (OR=2.777, 95% CI, 1.522-5.068; P=0.001). No significant heterogeneity was detected (Q=0.001, df=1, P=0.974). Tumor grade (OR=1.896, 95% CI, 0.487-7.383; P=0.357) was not associated with CD24 expression. Other clinicopathological parameters were not suitable for this meta-analysis.

Endometrial cancer. Two studies presented membranous and cytoplasmic CD24 expression as a function of clinicopathologic parameters in endometrial cancer patients (18,19). Membranous expression and cytoplasmic CD24 expression were found in 70 (56%) and 42 (33%) of 126 endometrial cancer patients, respectively. CD24 expression in the cytoplasm was observed in 30 (42%) of 71 cases with grades 2 or 3 and in 9 (20%) of 46 with grade 1. CD24 overexpression in the cytoplasm was significantly associated with high grade (OR=3.877, 95% CI, 1.548-9.715; P=0.004). There was no significant heterogeneity in two studies (Q=0.011, df=1, P=0.918). Myometrial invasion (OR=0.455, 95% CI, 0.193-1.077; P=0.073), lymph node metastasis (OR=10.420, 95% CI, 0.070-1550.767; P=0.359) and clinical stage (OR=3.629, 95% CI, 0.143-92.182; P=0.435) were not associated with cytoplasmic CD24 expression.

Biliary tract carcinoma. Three studies investigated CD24 expression in patients with carcinomas of the biliary tract including the gallbladder, common and hepatic bile ducts and ampulla of Vater (9,20,21). CD24 staining was found in 131 (55.5%) of 236 patients. Two studies compared CD24 expression between adenoma and carcinoma (9,21). CD24 overexpression was observed in 95 (57%) of 166 carcinoma patients and in 43 (41%) of 105 adenoma patients. CD24 expression was significantly greater in carcinoma than in adenoma (OR=2.015, 95% CI, 1.215-3.342; P=0.007). No significant heterogeneity was detected in two studies (Q=0.311, df=1, P=0.577). Other prognostic parameters were not available for this meta-analysis.

Colorectal cancer. Three (9,22,23) and two (9,23) studies described membranous and cytoplasmic staining of CD24, respectively, in colorectal cancers. Membranous expression and cytoplasmic expression of CD24 were detected in 188 (77%) of 244 and 137 (77%) of 178 patients, respectively. Two

studies compared membranous CD24 expression between adenoma and carcinoma (9,22). CD24 expression was not different between adenoma and carcinoma (OR=0.942, 95% CI, 0.330-2.695; P=0.912). Two studies compared cytoplasmic CD24 expression with lymph node metastasis (9,23). Cytoplasmic expression of CD24 was not associated with lymph node metastasis (OR=1.570, 95% CI, 0.704-3.503; P=0.271). Other parameters were not suitable for this meta-analysis.

Stomach cancer. Two studies presented CD24 expression in stomach cancers (9,24). Membranous and cytoplasmic expression of CD24 were observed in 106 (70%) and 60 (40%) of 151 patients, respectively. CD24 expression in the cytoplasm was not associated with lymph node metastasis (OR=1.825, 95% CI, 0.910-3.659; P=0.090). Other prognostic parameters were not available for this meta-analysis.

Discussion

Our results indicate that CD24 expression is significantly upregulated in different carcinomas compared to their benign lesions. In addition, in many human cancers CD24 overexpression is highly associated with adverse prognostic parameters such as lymph node metastasis, advanced clinical stages and worse overall survival.

This meta-analysis suggests that CD24 plays a role in carcinogenesis of the breast and ovary. CD24 expression was increased in breast and ovarian carcinomas with ORs of 14 and 9, compared to their benign lesions. In particular, the OR of cytoplasmic CD24 expression in breast and ovarian carcinomas were increased by ~36-fold each. CD24 expression in biliary tract carcinomas was also 2-fold greater than in biliary adenomas. However, CD24 expression was not different between colorectal adenomas and carcinomas. The results suggest that CD24 overexpression occurs at different stages of carcinogenesis in various organs. For example, it is hypothesized that upregulation of CD24 expression might occur in late stage breast and ovarian carcinogenesis but at early stages of the colorectal adenomacarcinoma sequence.

The mechanism by which CD24 induces tumorigenesis of hormone-dependent organs including the breast and ovary remains unknown. Recently, cancer stem cells in breast and prostate cancer have been represented as CD44⁺/CD24^{-low}, which resemble normal stem cells with respect to their ability to self-renew and to differentiate into diverse cell types (35,36,38). In contrast, Li *et al* (39) reported that CD44⁺/CD24⁺ pancreatic cancer cells exhibited stem cell properties. Therefore, CD24 is considered to be an important marker of cancer stem cells regardless of whether its expression is upregulated or downregulated.

In this meta-analysis, membranous or cytoplasmic CD24 overexpression was closely related to adverse factors such as lymph node metastases, advanced clinical stages and poor overall survival. However, the significance of CD24 overexpression was not consistent among carcinomas arising in different organs. CD24 expression was highly associated with lymph node metastases and lymphovascular invasions in breast and urothelial cancers, respectively, but not in

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rial, colorectal and gastric cancers. Additionally, expression was significantly related to advanced clinical stages in urothelial cancer, but not in breast and endometrial cancers.

In fact, CD24 on the cell membrane serves as a ligand for P-selectin and hence functions as an adhesion molecule that enhances platelet aggregation (1-3). CD24-expressing cancer cells can bind to P-selectin on the endothelial cells and platelets, leading to promotion of extravasation and metastasis of cancer cells (1-3). However, the exact nature of CD24 expression in the cytoplasm remains unknown and needs to be further elucidated. Several studies suggest that CD24 also participates in a signaling pathway via a regulator such as the chemokine receptor CXCR4 (1,2,33).

In summary, our study indicates that CD24 is an independent prognostic factor in many human cancers. In particular, CD24 may play a role in carcinogenesis, lymph node metastasis and/or local invasion in carcinomas of the breast, ovary and urinary bladder.

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