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Research Article

Mucin Expression in Bile Ducts Neoplasms - Systematic Review and Metaanalysis

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Abstract

Introduction: The definition of bile ducts tumours is not well-established, in particular this of mucin-producing neoplasms. Intraductal Papillary Neoplasm of the Bile Duct (IPNB) is a new term for pre neoplastic lesion leading to Cholangio Carcinoma (CC). Mucin expression may characterize this transformation and also be prognostic and predictive factor.

Aim: To compare different mucin genes expression in bile ducts lesions with normal bile duct epithelium.

Methods: English Medical literature searches were conducted for "mucin" and "bile ducts". Meta-analysis was performed by using Comprehensive metaanaslysis software. Pooled odds ratios and 95% confidence intervals were calculated.

Results: We found 298 eligible studies. 270 studies were rejected (performed in animals, not having full text, because of language, editorials, review articles, duplications). We were left with 28 studies including 4237 patients, from 6 countries that fulfilled the inclusion criteria, published till 31.7.2016. Mucin expression was significantly higher in bile ducts lesions than in normal epithelium with OR 6.81 (95%CI 3.88 – 11.93, P < 0.001). Measure of heterogeneity was moderate, demonstrated in the included studies: Q = 231.409, df (Q) = 61, P = 0.001, I^2= 73.64%. OR for mucin expression in CC and IPNB was 6.4 with 95% CI 2.5 – 16.5, P<0.001, and 6.9 with 95% CI 3.4 – 13.8, P<0.0001, respectively.

MUC1, *MUC2*, *MUC4*, and *MUC5AC* expression was significantly increased in bile ducts lesions.

Conclusion: According to the new classification and accumulated data on different CC type's behaviour, mucin genes expressions may serve as important clues for prognosis and prediction of treatment success.

Keywords: Mucin; Bile ducts; Gene Expression; Cholangiocarcinoma

Novelty & Impact Statements

In the first time we performed a metaanalysis and systematic review of mucin expression in malignant and pre malignant lesions of the bile ducts. *MUC1*, *MUC2*, *MUC4*, and *MUC5AC* expression was significantly increased in bile ducts lesions.

According to the new CC type's behaviour, mucin genes expression may serve as important clues for prognosis and prediction of treatment success.

Introduction

The definition of bile ducts tumours is not well-established, in particular this of mucin-producing neoplasms. Intraductal Papillary Neoplasm of the Bile Duct (IPNB) is a new term, equivalent to the Pancreatic Intraductal Papillary Mucinous Neoplasm (IPMN) [1]. Three phenotypes of IPNB were described: pancreatobiliary, intestinal and gastric. The expression of mucin in these lesions is different, *MUC1* in pancreatobiliary IPNB, *MUC2* in intestinal and *MUC5AC* in gastric types, respectively [2-4]. These mucins are also up-regulated when IPNB transforms into carcinoma, and their expression relates to aggressive behaviour, invasion and poorer prognosis, *MUC1* in ductal adenocarcinoma and *MUC5AC* in mucinous carcinoma.

The terms used in many studies are different and sometimes confusing. Cholangiocarcinoma (CC) may be ductal or mucinous, infiltrating or mass-forming. Sometimes investigators separate intrahepatic and extra hepatic CC, some discuss adenocarcinoma of the papilla as a separate entity and some not.

Very few studies described mucin expression in normal bile ducts. Sasaki et al found that the biliary epithelial cells switch *MUC1* apomucin expression before birth to *MUC3* after birth [5]. The same group found *MUC3* expression in CC and biliary epithelial dysplasia (similar to normal bile ducts), but a significant decrease of *MUC1* and *MUC2* expression [4]. In addition they described changes in *MUC1* and *MUC2* expression in the carcinogenesis process, from biliary intraepithelial neoplasia and IPNB into "tubular" adenocarcinoma (*MUC1* positive and *MUC2* negative), and colloid carcinoma (*MUC1* negative) [6].

Thus, a systematic review and metaanalysis may possibly clarify

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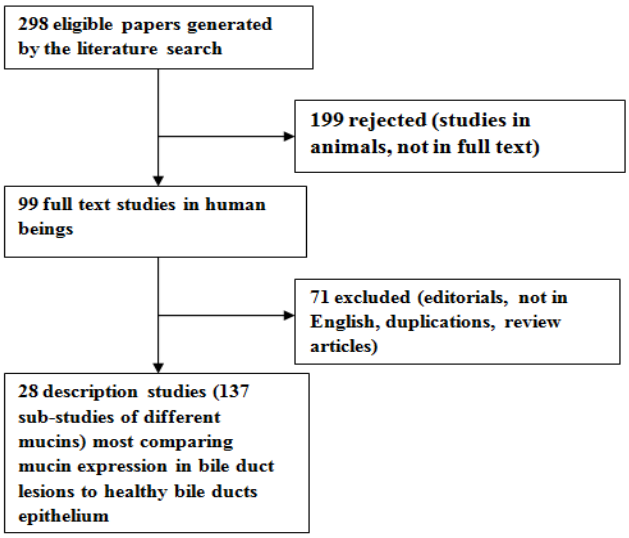


Figure 1: Flow chart of the articles identified for the metaanalysis.

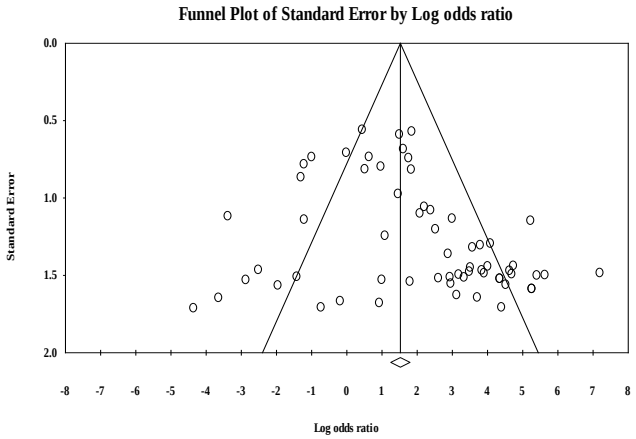


Figure 2: Funnel plot for publication bias.

the controversial results of observational studies and collect the knowledge about mucin expression in bile ducts lesions, trying to establish a role for different mucin expressions as prognostic markers.

Methods

Search strategy

English Medical literature searches were conducted for "mucin" and "bile ducts". Searches were performed through July 31th 2016, using MEDLINE, PubMed, Scopus, EMBASE and CENTRAL. Search terms were: "mucin" and "bile ducts". Hand searches of articles bibliography were also performed. Only fully published human studies in English were included (Figure 1).

Study selection

Observational studies describing mucin expression in bile ducts lesions were included. We selected only studies that clearly included cases of bile ducts lesions with or without comparison with normal tissue.

Data extraction

Name of the first author, year of the study publication, country of origin, number of patients with bile duct lesion that included in the study and the number of positive staining for a specific mucin were extracted. Then, data was stratified according to the lesion (CC or IPNB) and according to the mucin expressed (*MUC1, MUC2, MUC3, MUC4, MUC5AC, MUC5B, MUC6*, Tn antigen, sialyl Tn antigen, and T antigen).

Statistical analysis

Metaanalysis was performed by using Comprehensive metaanaslysis software (Version 3, Biostat Inc. and Englewood, NJ, United States). Pooled Odds Ratios (ORs) and 95% Confidence Intervals (CIs) were calculated for mucin expression in benign and malignant bile ducts lesions.

Heterogeneity between studies was evaluated using the Cochran *Q*-test, and it was considered to be present if the *Q*-test *P* value was less than 0.10. I^2 statistic was used to measure the proportion of inconsistency in individual studies. We also calculated a potential publication bias.

Study name	Subgroup within study	Outcome	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Yamashita K (I)	STn antigen IMH CC	Japan	1993	24.360	1.293	459.022	2.131	0.033
Yamashita K (I)	STn antigen IMH hepatolithiasis	Japan	1993	2.739	0.136	55.143	0.658	0.511
Yamashita K (I)	T antigen IMH CC	Japan	1993	6.333	1.271	31.568	2.252	0.024
Yamashita K (I)	T antigen IMH hepatolithiasis	Japan	1993	0.275	0.050	1.508	-1.487	0.137
Yamashita K (I)	Tn antigen IMH CC	Japan	1993	20.250	2.183	187.857	2.647	0.008
Yamashita K (I)	Tn antigen IMH hepatolithiasis	Japan	1993	8.100	0.932	70.369	1.896	0.058
Yamashita K (II)	MUC1 IMH CC	Japan	1993	0.302	0.032	2.834	-1.049	0.294
Yamashita K (II)	MUC1 IMH hepatolithiasis	Japan	1993	0.034	0.004	0.310	-3.004	0.003
Yamashita K (II)	MUC2 IMH CC	Japan	1993	0.300	0.064	1.398	-1.533	0.125
Yamashita K (II)	MUC2 IMH hepatolithiasis	Japan	1993	1.000	0.248	4.028	0.000	1.000
Sasaki M (I)	MUC1 IMH CC	Japan	1996	0.244	0.013	4.736	-0.932	0.352
Sasaki M (I)	MUC1 IMH dysplasia	Japan	1996	5.044	1.312	19.393	2.355	0.019
Sasaki M (I)	MUC2 IMH CC	Japan	1996	0.082	0.005	1.459	-1.703	0.089
Sasaki M (I)	MUC2 IMH dysplasia	Japan	1996	1.572	0.522	4.735	0.804	0.421
Sasaki M (I)	MUC3 IMH dysplasia	Japan	1996	0.057	0.003	1.159	-1.864	0.062
Sasaki M (II)	MUC1 IMH APCD	Japan	1996	23.000	0.942	561.790	1.923	0.054
Sasaki M (II)	MUC1 IMH multiple hepatic cysts	Japan	1996	41.400	1.644	1042.420	2.262	0.024
Sasaki M (II)	MUC1 IMH solitary hepatic cyst	Japan	1996	19.462	0.921	411.200	1.907	0.057
Sasaki M (III)	MUC1 ISH hepatolithiasis	Japan	1998	4.519	1.414	14.448	2.544	0.011
Sasaki M (III)	MUC2 ISH hepatolithiasis	Japan	1998	11.000	1.320	91.683	2.216	0.027
Sasaki M (III)	MUC3 ISH hepatolithiasis	Japan	1998	5.867	1.362	25.275	2.374	0.018
Sasaki M (III)	MUC5 ISH hepatolithiasis	Japan	1998	1.905	0.449	8.085	0.874	0.382
Lee KT	MUC2 ISH CC	Taiwan	2001	0.487	0.017	13.921	-0.420	0.674
Lee KT	MUC2 ISH hepatolithiasis	Taiwan	2001	3.000	0.260	34.575	0.881	0.378
Lee KT	MUC3 ISH CC	Taiwan	2001	0.013	0.000	0.375	-2.532	0.011
Lee KT	MUC4 ISH CC	Taiwan	2001	18.000	1.242	260.918	2.119	0.034
Lee KT	MUC4 ISH hepatolithiasis	Taiwan	2001	45.000	3.465	584.339	2.910	0.004
Lee KT	MUC5AC ISH CC	Taiwan	2001	82.333	2.881	2352.596	2.579	0.010
Lee KT	MUC5AC ISH hepatolithiasis	Taiwan	2001	12.600	1.186	133.892	2.101	0.036
Lee KT	MUC5B ISH CC	Taiwan	2001	0.026	0.001	0.669	-2.203	0.028
Ishikawa A	MUC2 IMH bile ducts stones	Taiwan	2004	2.667	0.556	12.794	1.226	0.220
Ishikawa A	MUC2 IMH CC	Taiwan	2004	0.143	0.007	3.089	-1.241	0.215
Ishikawa A	MUC2 IMH IPNL	Taiwan	2004	1.692	0.341	8.396	0.644	0.520
Ishikawa A	MUC2 IMH mucinous CC	Taiwan	2004	9.167	1.147	73.239	2.090	0.037
Ishikawa A	MUC5AC IMH bile ducts stones	Taiwan	2004	195.000	8.625	4408.558	3.314	0.001
Ishikawa A	MUC5AC IMH CC	Taiwan	2004	60.000	4.718	763.007	3.156	0.002
Ishikawa A	MUC5AC IMH IPNL	Taiwan	2004	195.000	8.625	4408.558	3.314	0.001
Ishikawa A	MUCAC IMH mucinous CC	Taiwan	2004	36.000	2.693	481.212	2.709	0.007
Shibahara H (I)	MUC1 IMH MPBT	Japan	2004	47.057	2.633	840.989	2.618	0.009
Shibahara H (I)	MUC2 IMH MPBT	Japan	2004	282.818	14.915	5362.820	3.760	0.000
Shibahara H (I)	MUC4 IMH MPBT	Japan	2004	103.435	5.761	1857.210	3.148	0.002
Shibahara H (I)	MUC5AC IMH MPBT	Japan	2004	188.500	19.782	1796.212	4.555	0.000
Shibahara H (I)	MUC6 IMH MPBT	Japan	2004	6.417	2.084	19.755	3.240	0.001
Shibahara H (II)	MUC1 IMH ICC-MF	Japan	2004	225.000	11.798	4291.038	3.601	0.000
Shibahara H (II)	MUC4 IMH ICC-MF	Japan	2004	33.000	1.816	599.537	2.363	0.018
Goto M	MUC6 IMH CC	Japan	2005	0.373	0.088	1.587	-1.334	0.182
Zen Y	MUC1 IMH>50% CC with BIEN	Japan	2006	93.000	4.339	1993.386	2.898	0.004
Zen Y	MUC1 IMH>50% CC with IPNL	Japan	2006	6.097	0.296	125.550	1.171	0.241
Zen Y	MUC2 IMH>50% BIEN	Japan	2006	0.840	0.032	22.167	-0.104	0.917
Zen Y	MUC2 IMH>50% CC with IPNL	Japan	2006	28.412	1.454	555.092	2.207	0.027
Zen Y	MUC2 IMH>50% IPNL	Japan	2006	78.273	3.940	1555.077	2.859	0.004
Zen Y	MUC5AC IMH>50% BIEN	Japan	2006	50.217	2.710	930.473	2.629	0.009
Zen Y	MUC5AC IMH>50% CC with BIEN	Japan	2006	13.696	0.694	270.299	1.720	0.085
Zen Y	MUC5AC IMH>50% CC with IPNL	Japan	2006	19.000	0.975	370.227	1.943	0.052
Zen Y	MUC5AC IMH>50% IPNL	Japan	2006	78.273	3.940	1555.077	2.859	0.004
Hughes NR	MUC2 IMH CC	Australia	2010	2.556	0.095	68.999	0.558	0.577
Hughes NR	MUC5AC IMH CC	Australia	2010	110.200	5.874	2067.283	3.144	0.002
Hughes NR	MUC6 IMH CC	Australia	2010	4.364	0.642	29.641	1.507	0.132
Higashi M (II)	MUC1 IMH CC	Japan	2012	1350.818	73.091	24965.050	4.844	0.000
Higashi M (II)	MUC16 IMH CC	Japan	2012	115.627	6.854	1950.754	3.295	0.001
Higashi M (II)	MUC2 IMH CC	Japan	2012	33.950	1.970	585.029	2.427	0.015
Higashi M (II)	MUC4 IMH CC	Japan	2012	55.652	3.274	946.018	2.780	0.005
				6.807	3.884	11.930	6.700	0.000

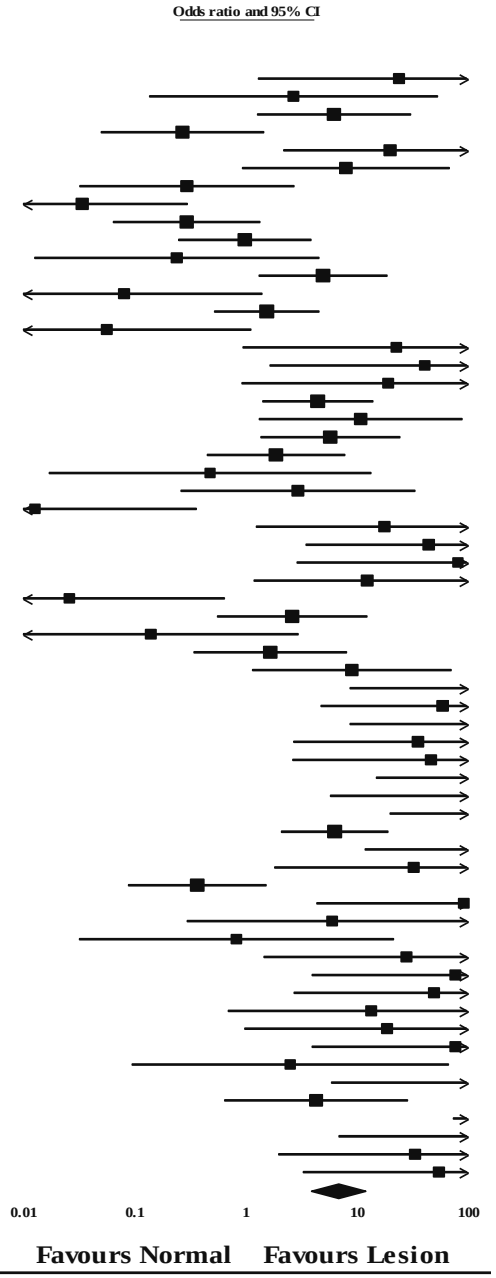
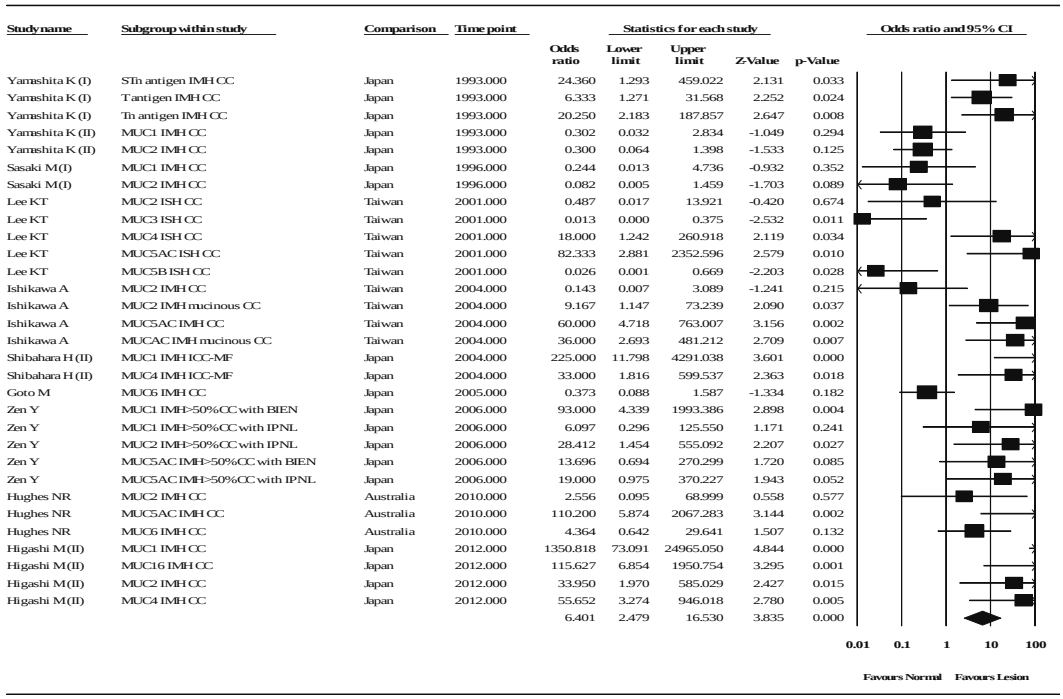


Figure 3: Metaanalysis of mucin expression in bile ducts lesions (28 studies, 137 sub-studies).
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

Results

All together we found 298 eligible studies. 199 studies were rejected because they were performed in animals or not having full text and 71 studies were excluded because of language, being editorials, review articles or because of duplications. We were left with 28 observational studies including 4237 patients, from 6 countries (Japan, Taiwan, Korea, South Africa, Australia and USA) that fulfilled the inclusion criteria, published till 31.7.2016 [2-30] (Figure 1). There are 137 sub-studies (stratifying data according to mucin types and lesions). In 122 sub-studies Immunohistochemistry (IMH) has been used and in 15 sub-studies *In Situ* Hybridization (ISH) for RNA. Twelve studies and 71 sub-studies (1454 patients) had also results of normal bile ducts epithelium for comparison with the neoplastic lesion. Cholangiocarcinoma was examined in 87 sub-studies and benign biliary lesions, such as IPNB, cysts or hepatolithiasis in 50 sub-studies. Funnel plot denies a significant publication bias (Figure 2).



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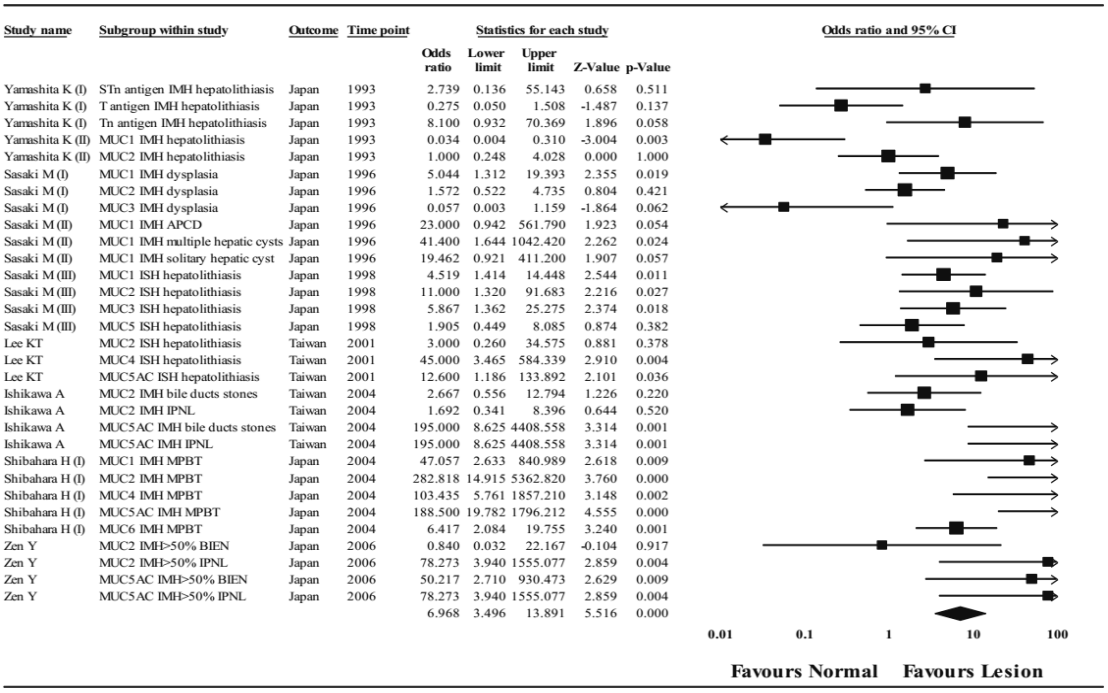
Higashi M (II)	MUC4 IMH CC	Japan	2012.000	55.652	3.274	946.018	2.780	0.005
				6.401	2.479	16.530	3.835	0.000

Figure 4a: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different lesions: cholangiocarcinoma (89 sub-studies).
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma



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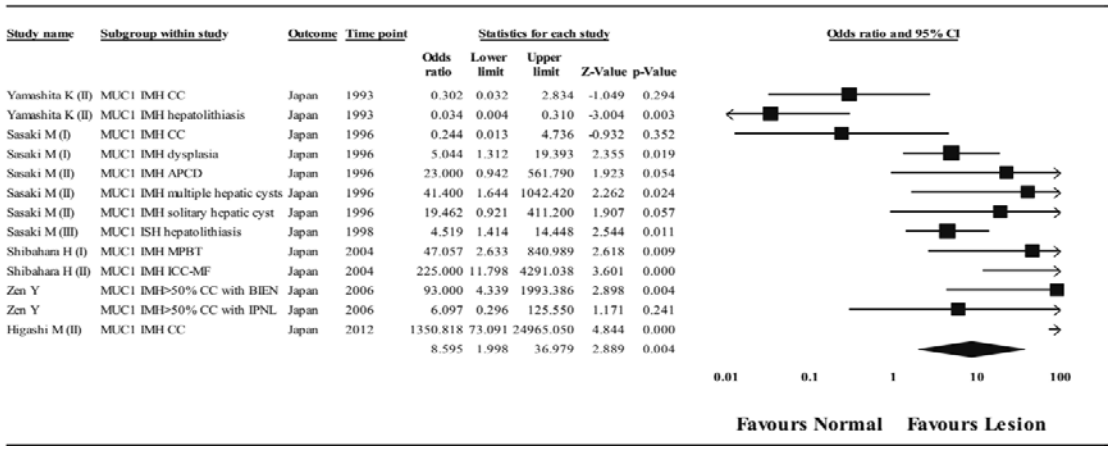
Shibahara H (I)	MUC4 IMH MPBT	Japan	2004	103.435	5.761	1857.210	3.148	0.002
Shibahara H (I)	MUC5AC IMH MPBT	Japan	2004	188.500	19.782	1796.212	4.555	0.000
Shibahara H (I)	MUC6 IMH MPBT	Japan	2004	6.417	2.084	19.755	3.240	0.001
Zen Y	MUC2 IMH>50% BIEN	Japan	2006	0.840	0.032	22.167	-0.104	0.917
Zen Y	MUC2 IMH>50% IPNL	Japan	2006	78.273	3.940	1555.077	2.859	0.004
Zen Y	MUC5AC IMH>50% BIEN	Japan	2006	50.217	2.710	930.473	2.629	0.009
Zen Y	MUC5AC IMH>50% IPNL	Japan	2006	78.273	3.940	1555.077	2.859	0.004
				6.968	3.496	13.891	5.516	0.000

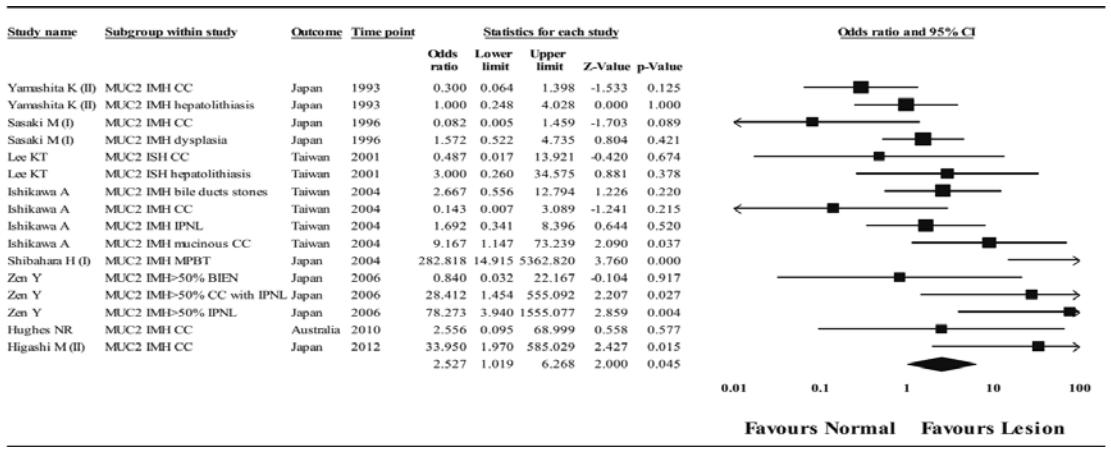
Figure 4b: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different lesions: IPMB (48 sub-studies).
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

In the random-effect model, mucin expression was significantly higher in bile ducts lesions than in normal epithelium with OR 6.81 (95% CI 3.88-11.93, P < 0.001) (Figure 3). Measure of heterogeneity was moderate, demonstrated in the included studies: Q = 231.409, df



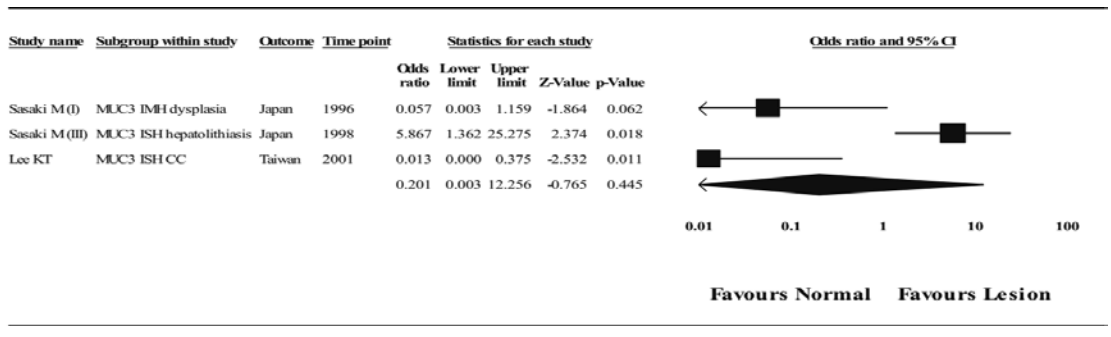
Study name	Subgroup within study	Outcome	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Yamashita K (II)	MUC1 IMH CC	Japan	1993	0.302	0.032	2.834	-1.049	0.294
Yamashita K (II)	MUC1 IMH hepatolithiasis	Japan	1993	0.034	0.004	0.310	-3.004	0.003
Sasaki M (I)	MUC1 IMH CC	Japan	1996	0.244	0.013	4.736	-0.932	0.352
Sasaki M (I)	MUC1 IMH dysplasia	Japan	1996	5.044	1.312	19.393	2.355	0.019
Sasaki M (II)	MUC1 IMH APCD	Japan	1996	23.000	0.942	561.790	1.923	0.054
Sasaki M (II)	MUC1 IMH multiple hepatic cysts	Japan	1996	41.400	1.644	1042.420	2.262	0.024
Sasaki M (II)	MUC1 IMH solitary hepatic cyst	Japan	1996	19.462	0.921	411.200	1.907	0.057
Sasaki M (III)	MUC1 ISH hepatolithiasis	Japan	1998	4.519	1.414	14.448	2.544	0.011
Shibahara H (I)	MUC1 IMH MPBT	Japan	2004	47.057	2.633	840.989	2.618	0.009
Shibahara H (II)	MUC1 IMH ICC-MF	Japan	2004	225.000	11.798	4291.038	3.601	0.000
Zen Y	MUC1 IMH>50% CC with BIEN	Japan	2006	93.000	4.339	1993.386	2.898	0.004
Zen Y	MUC1 IMH>50% CC with IPNL	Japan	2006	6.097	0.296	125.550	1.171	0.241
Higashi M (II)	MUC1 IMH CC	Japan	2012	1350.818	73.091	24965.050	4.844	0.000
				8.595	1.998	36.979	2.889	0.004

Figure 5a: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: MUC1.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma



Study name	Subgroup within study	Outcome	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Yamashita K (II)	MUC2 IMH CC	Japan	1993	0.300	0.064	1.398	-1.533	0.125
Yamashita K (II)	MUC2 IMH hepatolithiasis	Japan	1993	1.000	0.248	4.028	0.000	1.000
Sasaki M (I)	MUC2 IMH CC	Japan	1996	0.082	0.005	1.459	-1.703	0.089
Sasaki M (I)	MUC2 IMH dysplasia	Japan	1996	1.572	0.522	4.735	0.804	0.421
Lee KT	MUC2 ISH CC	Taiwan	2001	0.487	0.017	13.921	-0.420	0.674
Lee KT	MUC2 ISH hepatolithiasis	Taiwan	2001	3.000	0.260	34.575	0.881	0.378
Ishikawa A	MUC2 IMH bile ducts stones	Taiwan	2004	2.667	0.556	12.794	1.226	0.220
Ishikawa A	MUC2 IMH CC	Taiwan	2004	0.143	0.007	3.089	-1.241	0.215
Ishikawa A	MUC2 IMH IPNL	Taiwan	2004	1.692	0.341	8.396	0.644	0.520
Ishikawa A	MUC2 IMH mucinous CC	Taiwan	2004	9.167	1.147	73.239	2.090	0.037
Shibahara H (I)	MUC2 IMH MPBT	Japan	2004	282.818	14.915	5362.820	3.760	0.000
Zen Y	MUC2 IMH>50% BIEN	Japan	2006	0.840	0.032	22.167	-0.104	0.917
Zen Y	MUC2 IMH>50% CC with IPNL	Japan	2006	28.412	1.454	555.092	2.207	0.027
Zen Y	MUC2 IMH>50% IPNL	Japan	2006	78.273	3.940	1555.077	2.859	0.004
Hughes NR	MUC2 IMH CC	Australia	2010	2.556	0.095	68.999	0.558	0.577
Higashi M (II)	MUC2 IMH CC	Japan	2012	33.950	1.970	585.029	2.427	0.015
				2.527	1.019	6.268	2.000	0.045

Figure 5b: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: MUC2.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma



Study name	Subgroup within study	Outcome	Time point	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Sasaki M (I)	MUC3 IMH dysplasia	Japan	1996	0.057	0.003	1.159	-1.864	0.062
Sasaki M (III)	MUC3 ISH hepatolithiasis	Japan	1998	5.867	1.362	25.275	2.374	0.018
Lee KT	MUC3 ISH CC	Taiwan	2001	0.013	0.000	0.375	-2.532	0.011
				0.201	0.003	12.256	-0.765	0.445

Figure 5c: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: MUC3.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

(Q) = 61, P = 0.001, I^2= 73.64%.

OR for mucin expression in CC and IPNB was 6.4 with 95% CI 2.5-16.5, P<0.001, and 6.9 with 95%CI 3.4-13.8, P<0.0001, respectively (Figures 4a, 4b).

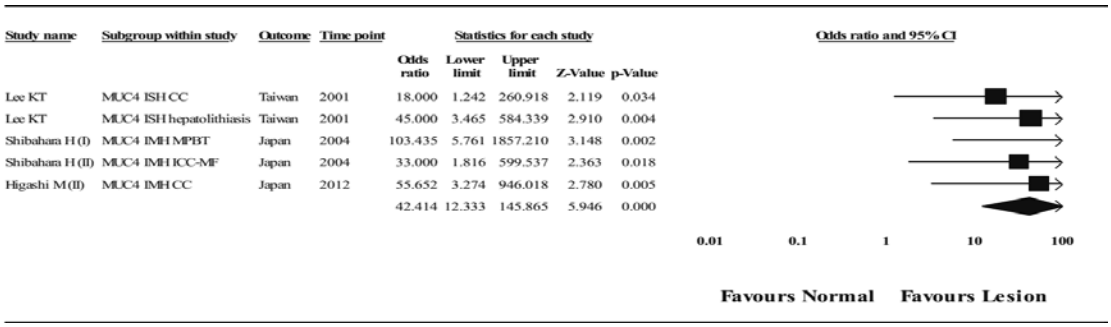


Figure 5d: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: MUC4.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

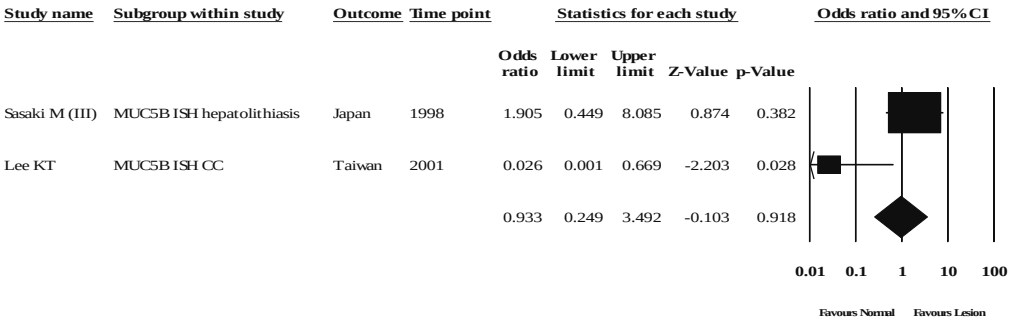


Figure 5e: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: MUC5AC.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

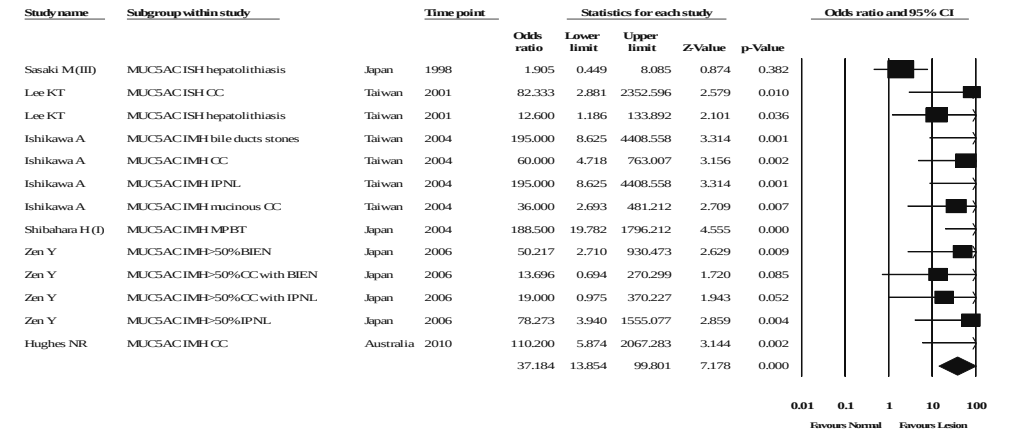


Figure 5f: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: MUC5B.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

OR for total expression in bile ducts lesion of *MUC1, MUC2, MUC3, MUC 4, MUC5AC, MUC5B, MUC6*, Tn antigen, STn antigen and T antigen, was **8.5** with 95% CI 1.9-36.9, P = 0.004; **2.5** with 95% CI 1.0-6.2, P = 0.045; **0.2** with 95% CI 0.003-12.256, P = 0.445; **42.4** with 95% CI 12.3-145.8, P < 0.0001; **37.1** with 95% CI 13.8-99.8, P < 0.0001; **0.289** with 95% CI 0.005-18.569, P < 0.559; **2.1** with 95% CI 0.3-14.0, P = 0.410; **12.6** with 95% CI 2.6-59.6, P-0.001; **8.3** with 95% CI 0.9-71.1, P=0.052, and **1.3** with 95% CI 0.062-29.950, p=0.853, respectively (Figures 5a, 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j) (Table 1).

Studies Description

Sasaki et al found a decrease in *MUC1* and *MUC2* expression in CC [4-6].

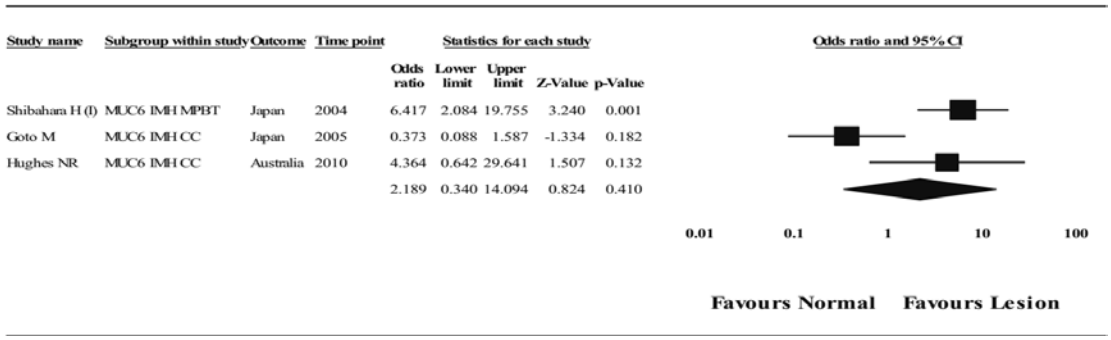


Figure 5g: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: MUC6.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

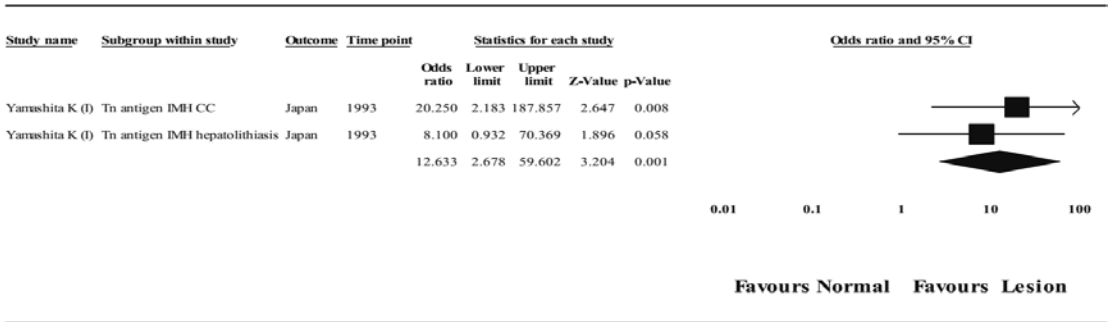


Figure 5h: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: Tn antigen.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

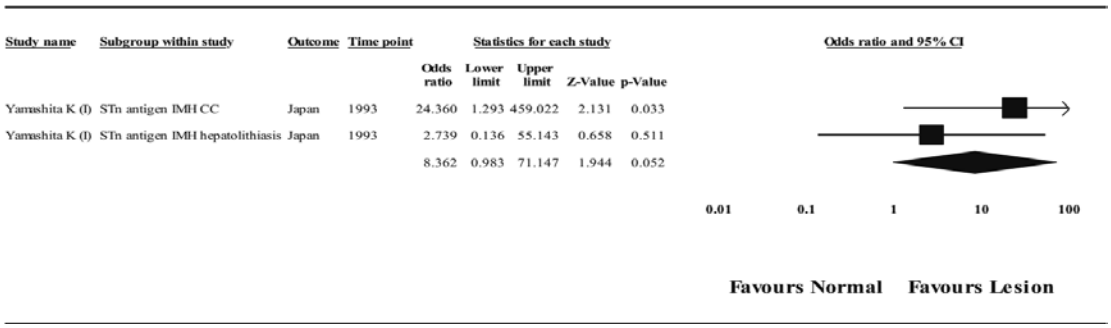


Figure 5i: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: STn antigen.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

Higashi et al described 3 different patterns of CC [7]. *MUC1* expression was associated with poor outcome, while expression of *MUC2* was a favorable prognostic indicator. Amaya et al found that biliary papillomatosis could undergo overt malignant transformation along with altered phenotypic expression of *MUC1, MUC2* and tumor antigens Tn and Sialyl Tn (STn) [3]. Expression of *MUC2* and STn, decreased and increased respectively, in CC**.** Matsumura et al found a positive correlation between *MUC1* expression and bad prognosis in mass forming intrahepatic CC, especially when the cytoplasm of the cancer cells was stained positive [8]. Ishikawa et al described an increased expression of *MUC2* in normal bile ducts of patients with biliary stones, similar to that found in intraductal papillary neoplasm and mucinous Cholangiocarcinoma [9]. Goto et al could not demonstrate a difference in *MUC6* expression between CC and normal bile ducts [2]. Hong et al studied 193 patients with CC, and found that *MUC2* expression was a good prognostic factor [10]. The opposite was demonstrated for *MUC4* and *MUC1* [11]. Zen et al found increased expression of *MUC1* in ductal CC, but not in colloid carcinoma, in patients with hepatolithiasis [12]. Higashi et al found that *MUC16* expression is a prognostic factor of

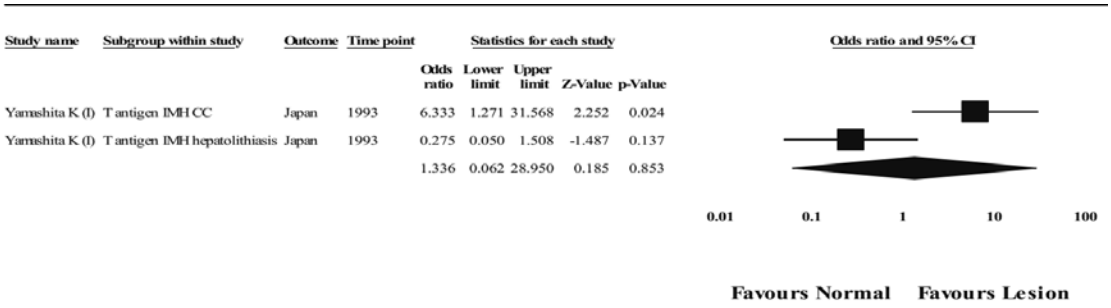


Figure 5j: Metaanalysis of mucin expression in bile ducts lesions, sub-studies of different mucins: T antigen.
CC: Cholangiocarcinoma; BP: Biliary Papilomatosis; IMH: Immunocytochemistry; IPNL: IPNB: Intraductal Papillary Neoplasm of the Liver; BIEN: BilIN: Biliary Intraepithelial Neoplasia; ISH: *In Situ* Hybridization; APCD: Adult-Type Polycystic Disease; MPBT: Mucin Producing Bile Duct Tumor; ICC-MF: Intrahepatic Cholangiocarcinoma-Mass Forming Type; MF-CC: Mass Forming Cholangiocarcinoma

Table 1: Summary of mucin expression in bile ducts lesions.

Mucin gene	OR of mucin expression	P
MUC1	8.5	0.004
MUC2	2.5	0.045
MUC3	0.2	NS
MUC4	42.4	<0.0001
MUC5AC	37.1	<0.0001
MUC5B	0.2	NS
MUC6	2.1	NS
Tn antigen	12.6	0.001
STn antigen	8.3	0.052
T antigen	1.3	NS
Total mucin	6.8	<0.0001

OR = odds ratio

poor survival in CC [13]. *MUC1* expression was found in 100% of 21 cases of CC by Xu et al, and was associated with cell adhesion and invasive ability [14]. Sasaki et al looked at mucin expression using in situ hybridization [15]. The intramural and extramural peri biliary glands in hepatolithiasis expressed *MUC3* and *MUC6* apomucins and focally expressed *MUC2* and *MUC5* apomucins. These mucins could be involved in hepatolithiasis. They also found expression of *MUC1* in the late cystogenetic process of the liver [16]. Yeh et al found a better survival for CC patients without expression of *MUC4* [17]. Yamashita et al found that expression of Tn and sialyl Tn antigens of mucin are indicators of malignancy in the intrahepatic bile ducts [18]. Shibahara et al found *MUC1* expression in the invasive growth of CC with disappearing of *MUC2* [19]. The same group demonstrated that expression of *MUC4* in intrahepatic Cholangiocarcinoma-mass forming type is an independent factor for poor prognosis and is a useful marker to predict outcome [20]. Aishima et al divided 100 cases of CC according to mucin expression into null type, gastric foveolar type, pyloric gland type and gastric combined type [21]. Gastric foveolar type was associated with aggressive tumour behaviour. Lee and Liu demonstrated that neoplastic transformation of the biliary epithelium is accompanied by increased expression of *MUC4* and *MUC5AC* [22]. Mall et al found a positive correlation between *MUC1* and metastasis in CC, and a negative correlation with *MUC3* [23]. *MUC5AC* expression was found to be an independent predictor of poor prognosis in patients who underwent hepatectomy for mass forming CC [24]. Hughes et al found a similar mucin expression pattern in bile duct adenoma to the expression of mucins in the stomach [25]. Onoe et al found that papillary Cholangiocarcinoma that produced mucin (*MUC1*, *MUC2*, *MUC5AC*, and *MUC6*) was similar in prognosis and morphology to non-mucin producing papillary Cholangiocarcinoma [26]. Aquaporin-1is responsible for water transport across bile duct epithelium [27]. Its expression was found to inversely correlate with that of mucus core protein *MUC5AC* in CC, and their distribution tended to be complementary. Sasaki et al found that over expression of enhancer of *MUC1* may be related to malignant behaviour in intraductal papillary neoplasm of the bile duct [28]. Lok et al found *MUC5AC* in 12% of CC patients [29]. Tamada et al found that *MUC1*core peptide was the most useful prognosis indicator among the various glycoforms of *MUC1* mucins [30]. In contrast, the expression of *MUC2* was inversely related with the tumor progression factors and poor outcome.

Discussion

MUC1, *MUC2*, *MUC4*, *MUC5AC* and Tn antigen were up regulated and had significantly higher expression in IPNB and CC than in normal bile ducts epithelium in our metaanalysis. Thus, these mucins may play a role in the transformation from normal epithelium to IPNB and CC; serve as markers for early detection and therapeutic targets. This is also an important argument for hepatolithiasis and IPNB being pre malignant states and precursors of CC and mucinous bile ducts carcinoma.

Up regulation of *MUC1* was associated with poor prognosis, while expression of *MUC2* and *MUC3* was a favorable prognostic indicator [7,8,10,11,14,19,23,28,30]. *MUC4* and *MUC5AC* were also bad prognostic factors when expressed in CC [11,17,22,31]. *MUC4*, an intra membrane ligand for the tyrosine kinase receptor ErbB2, is related with regulation of p27 [20]. The patients with CC positive for *MUC4* showed a short survival period compared to non-expressing patients.

Increased expression of *MUC5AC* in the serum in CC patients was also found to be significantly higher than in benign bile ducts pathologies [32,33]. Serum *MUC5AC* was associated with advanced CC. The determination of serum *MUC5AC* may be predictive of poor prognosis and may be useful in selecting treatment options.

The weakness of our systematic review and metaanalysis is in the lack of homogeneity between studies neither in regard to bile ducts lesions definition nor in using the same methods for evaluation of mucin expression. Cholangiocarcinoma comprises a heterogeneous group of cancers with different types of biliary tract differentiation, and arises from the intra- or extra hepatic biliary tract. On the basis of its origin, CC was recently classified as intrahepatic, peri hilar, or distal CC [31]. This classification had no expression in our review. In addition, the prevalence of CC is very different in the east and west. An example is the very high prevalence of 80 per 100,000 population in Northeast Thailand, and much lower rates in Canada of only 0.3 per 100,000 [31]. In conclusion, a new era of investigations is now open in the field of CC. According to the new classification and accumulated data on different CC type's behaviour, mucin genes may serve as important clues for prognosis and prediction of treatment success.

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