

Keywords: cervical cancer; peritoneal cytology; prognosis; meta-analysis

The impact of positive peritoneal cytology on prognosis in patients with cervical cancer: a meta-analysis

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Background: The impact of positive peritoneal cytology on the prognosis of cervical cancer is controversial. Thus, we performed a meta-analysis to determine its impact on recurrence, and to investigate correlations between abnormal cytology and/or lymph node metastasis in cervical cancer.

Methods: A systematic literature review was conducted through July 2014. Odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated by standard meta-analysis techniques with the fixed-effects models, if there was no significant statistical heterogeneity across studies by using I^2 .

Results: Of 303 studies retrieved, 6 were included in the meta-analysis. These six case–control observational studies included 1360 cervical cancer patients who showed negative peritoneal cytology and 64 who showed positive peritoneal cytology. Over the combined study period, 20 of 45 in the positive peritoneal cytology group experienced recurrence, whereas 88 of 539 controls did. The meta-analysis based on the fixed-effects model indicated a significant increase in the risk of recurrence in the positive peritoneal cytology group relative to the control group (OR: 4.47; 95% CI: 2.33–8.58, $P < 0.001$, $I^2 = 0.0\%$). Moreover, the results of our meta-analysis suggested that the positive peritoneal cytology group displayed more lymph node metastasis than the negative peritoneal cytology group (OR: 3.73; 95% CI: 2.13–6.53, $P < 0.001$, $I^2 = 0.0\%$).

Conclusions: Although based mainly on retrospective observational studies, our meta-analysis indicates that abnormal peritoneal cytology may be strongly associated with poor prognosis in patients with cervical cancer. Future research should verify this relationship through prospective observational studies over a longer term.

Peritoneal cytology examination is commonly performed for samples obtained during gynecology surgery. The prognostic value of peritoneal cytology in ovarian cancer among gynaecological neoplasms is widely accepted, and it is included in the International Federation of Gynecology and Obstetrics (FIGO) nomenclature (1994) (Benedet *et al*, 2003). In endometrial carcinoma, peritoneal cytology is included in the FIGO staging system, and positive cytology must be reported separately without changing the stage. A positive cytology result is considered a poorer prognostic factor. However, only a few reports have addressed the issue of positive peritoneal cytology in cervical

neoplasms (Benedet *et al*, 2003; Kuji *et al*, 2014). In cervical cancer, the incidence of positive peritoneal cytology has been reported to be 0–15% (Kilgore *et al*, 1984; Delgado *et al*, 1989; Takeshima *et al*, 1997; Estape *et al*, 1998; Kasamatsu *et al*, 2009). It is reported that the rate of positive peritoneal cytology among patients with squamous cell carcinoma (SCC) in FIGO stage I or II disease is low (0.3–1.8%) (Delgado *et al*, 1989; Takeshima *et al*, 1997; Estape *et al*, 1998). On the other hand, positive peritoneal cytology was found four times more frequently in adenocarcinoma (ADC) than in SCC (Imachi *et al*, 1987). However, the prognostic value of peritoneal cytology in cervical carcinoma remains unanswered.

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Previous reports have been inconsistent; whereas one study failed to show any prognostic inference of positive peritoneal cytology in cervical cancer (Abu-Ghazaleh *et al*, 1984; Delgado *et al*, 1989; Trelford *et al*, 1995; Takeshima *et al*, 1997), other studies reported that patients with positive peritoneal cytology have a poor prognosis than those with negative cytology (Imachi *et al*, 1987; Ito and Noda, 1992; Kashimura *et al*, 1997; Estape *et al*, 1998; Zuna *et al*, 2009). Furthermore, some studies reported that positive peritoneal cytology was associated with poor prognosis only in the patients with ADC or adenosquamous carcinoma, but not in those with SCC (Kasamatsu *et al*, 2009; Kuji *et al*, 2014).

Therefore, we performed a meta-analysis using relevant studies to investigate the impact of positive peritoneal cytology on prognosis, focusing on lymph node metastasis and experienced recurrence, in cervical carcinoma when compared with negative peritoneal cytology.

MATERIALS AND METHODS

Search strategy. Two of the authors of the present study (S-HY and S-HS) designed the protocol and extraction forms in accordance with the Preferred Reporting Items for systematic Review and Meta-analyses (PRISMA) guideline. For this meta-analysis, we searched online abstracts from PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library through July 2014. For this search, we used the following keywords: 'cervical neoplasm or cancer or carcinoma or malignancy,' 'uterine cervical neoplasm or cancer or carcinoma or malignancy,' 'carcinoma of the cervix or the uterine cervix,' 'invasive carcinoma of the cervix or the uterine cervix,' 'squamous cell carcinoma of the cervix or the uterine cervix,' 'adenocarcinoma of the cervix or the uterine cervix,' and 'positive intra-peritoneal cytology or positive peritoneal washing cytology or abnormal cytology.' The titles and abstracts were checked to exclude any clearly unrelated articles. The full text of the remaining papers was evaluated to determine their relevance. In addition, the references cited in the selected papers and published reviews were checked to evaluate whether they included any additional studies of relevance.

Selection criteria. Studies were included if (1) they were randomised controlled trials, a prospective or retrospective cohort study, a population-based case-control study, or a nested case-control study; (2) the participants of interest received surgical treatment for cervical cancer; (3) the intervention of interest was peritoneal cytology; (4) the outcome measured was cervical cancer recurrence and/or lymph node metastasis, measured as the relative risk, the odds ratio (OR), or the hazard ratio estimated with the 95% confidence interval (CI) (or sufficient data for calculating them). Single-arm cohort studies were not included in the meta-analysis. The studies that included advanced stage disease, such as stage III or IV, were excluded from the meta-analysis.

Data extraction. Data from each included study were systematically extracted by two authors using a standardised form. The form documented the most relevant items, including the name of the first author, the year of publication, the study design, the study period, age, sample size (cases and controls or cohort size), tumour stage, histological type, peritoneal cytology positivity, follow-up period, and prognostic value (recurrence, lymph node metastasis) between positive and negative peritoneal cytology.

Quality assessment. Study quality was evaluated independently by two authors using the nine-star Newcastle-Ottawa scale (NOS) criteria (Stang, 2010). The NOS criteria included three categories: (1) selection: 0–4; (2) comparability: 0–2; (3) exposure (case-control studies) or outcomes (cohort studies): 0–3. NOS scores ranged from 0 to 9, with a score ≥ 7 indicating good quality. Any

disagreement was resolved after a discussion and reevaluation with the third author.

Statistical analysis. From the original study data, the OR and the 95% CI were calculated for each study for the recurrence rate for positive and negative peritoneal cytology (Higgins and Thompson, 2002). Heterogeneity across studies was examined using I^2 , which measures the percentage of the total variation across studies. Here substantial heterogeneity was defined as an I^2 -value $> 50\%$ (Higgins *et al*, 2003). In the absence of significant heterogeneity, a fixed-effects model was used. When there was statistical heterogeneity, a random-effects model was used to estimate the combined OR for randomised and observational studies. Then, a subgroup analysis was conducted for the type of histology (SCC, ADC, or all type). The subgroup analysis was planned *a priori* before the data were collected and analysed. To evaluate the influence of single studies on the overall estimate, a sensitivity analysis was performed. Publication bias was evaluated using a graphical method. A funnel plot was built to assess this bias by using the s.e. and the OR (Sterne and Egger, 2001; Sterne *et al*, 2001). Publication bias was evaluated using the Begg–Mazumdar rank correlation test, Egger's test and the fail-safe N -test (Orwin and Boruch, 1983; Begg and Mazumdar, 1994). Comprehensive Meta-Analysis version 2.0 (Biostat, Englewood, NJ, USA) was used for all statistical tests. $P < 0.05$ was considered significant for this meta-analysis. Data from this meta-analysis are presented according to the checklist based on the Meta-analysis Of Observational Studies in Epidemiology (Stroup *et al*, 2000).

RESULTS

Literature search. Figure 1 presents a flow diagram showing how relevant studies were identified. A total of 22 potentially relevant papers were found by focusing on abnormal peritoneal cytology and prognosis, particularly recurrence or lymph node metastasis (Creasman and Rutledge, 1971; Keettel *et al*, 1974; Hughes *et al*, 1980; Abu-Ghazaleh *et al*, 1984; Kilgore *et al*, 1984; Ziselman *et al*, 1984; Willett, 1985; Roberts *et al*, 1986; Imachi *et al*, 1987; Delgado *et al*, 1989; Zuna *et al*, 1990; Ito and Noda, 1992; Morris *et al*, 1992; Patsner, 1992; Trelford *et al*, 1995; Zuna and Behrens, 1996; Zuna, 1996; Kashimura *et al*, 1997; Takeshima *et al*, 1997; Estape *et al*, 1998; Kasamatsu *et al*, 2009; Kuji *et al*, 2014). Among these 22 papers, 16 were excluded: seven papers were incomplete studies providing no exact recurrence data (Abu-Ghazaleh *et al*, 1984; Kilgore *et al*, 1984; Zuna *et al*, 1990; Morris *et al*, 1992; Patsner, 1992; Trelford *et al*, 1995; Estape *et al*, 1998), one paper was a letter to the editor (Zuna, 1996), and another five studies lacked relevance to prognosis and cervical cancer (Creasman and Rutledge, 1971; Hughes *et al*, 1980; Ziselman *et al*, 1984; Willett, 1985; Zuna and Behrens, 1996); three studies included patients who underwent surgical treatment at advanced stages (Keettel *et al*, 1974; Roberts *et al*, 1986; Imachi *et al*, 1987). The remaining six studies reported on abnormal peritoneal cytology and prognosis and, thus, were included in the meta-analysis (Delgado *et al*, 1989; Ito and Noda, 1992; Kashimura *et al*, 1997; Takeshima *et al*, 1997; Kasamatsu *et al*, 2009; Kuji *et al*, 2014).

Study characteristics. After the final screening of the six relevant retrospective case-control observational studies, 1424 patients were enrolled in this meta-analysis, including a total of 64 cervical cancer patients with positive peritoneal cytology and 1360 with negative cytology. Publication years of the eligible studies ranged from 1989 to 2014. The studies were from the United States and Japan, and were assessed to range from 7 to 8 on the nine-star NOS. Table 1 shows the study characteristics in detail.

All of the patients had FIGO stage IA-IIIB disease. Most histologic types, in particular, SCC, ADC and adenosquamous

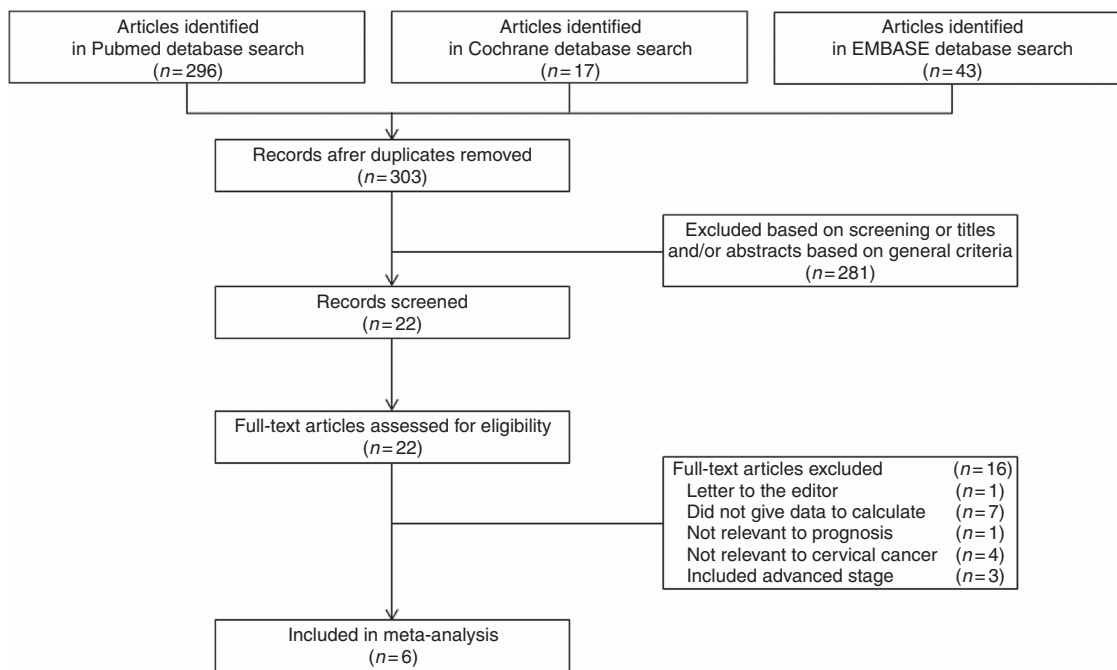


Figure 1. Flow diagram of the procedure for the literature search.

carcinoma, were included in each study, with the exception of two studies. Specifically, one study included only ADC histologic type (Kasamatsu *et al*, 2009) and another, only SCC (Delgado *et al*, 1989). Among all patients, 1360 (95.5%) showed negative peritoneal cytology, whereas positive peritoneal cytology was observed in 64 (4.5%).

Meta-analysis. Three studies (Ito and Noda, 1992; Takeshima *et al*, 1997; Kasamatsu *et al*, 2009) included a total of 584 patients with a combined total of 108 recurrences (20 of which occurred in the 45 patients with positive peritoneal cytology). Figure 2A shows the ORs for cervical cancer recurrence for each study, and for all studies combined, comparing the positive peritoneal cytology with negative cytology. As no heterogeneity existed among studies ($P=0.473$ and $I^2=0\%$), the fixed-effects model was used. The pooled OR for positive peritoneal cytology and the risk of cervical cancer recurrence was 4.468 (95% CI: 2.326–8.583, $P<0.001$).

There were six studies (Delgado *et al*, 1989; Ito and Noda, 1992; Kashimura *et al*, 1997; Takeshima *et al*, 1997; Kasamatsu *et al*, 2009; Kuji *et al*, 2014), including 1424 patients with a combined total of 317 lymph node metastases (34 of which occurred in the 64 patients with positive peritoneal cytology). Figure 2B shows the ORs for lymph node metastasis for each study, and for all studies combined, comparing positive peritoneal cytology with negative cytology. As no heterogeneity existed among studies ($P=0.606$ and $I^2=0\%$), the fixed-effects model was used. The pooled OR for positive peritoneal cytology and the risk of lymph node metastasis was 3.726 (95% CI: 2.127–6.525, $P<0.001$).

In the sensitivity analysis, the results based on the omission of one study at a time and the calculation of the pooled OR for the remaining studies showed that no study had a significant effect on the pooled OR (Figure 3A and B).

Subgroup analysis by the type of histology. Figure 4A and B shows the OR for each study and the pooled OR for categories of ADC (including adenosquamous carcinoma), SCC, and ADC (including adenosquamous carcinoma) plus SCC. Positive peritoneal cytology in ADC-type cervical cancer led to a significant increase in recurrence (OR: 3.684; 95% CI: 1.680–8.077; $P=0.001$ and $I^2=0\%$). Positive peritoneal cytology in cervical cancer with

the ADC plus SCC histological type was also associated with recurrence (OR: 9.667; 95% CI: 2.132–43.829; $P=0.003$ and $I^2=0\%$). Although only one study (Takeshima *et al*, 1997) reported on the SCC histological type (OR: 1.701; 95% CI: 0.172–16.780; $P=0.649$ and $I^2=0\%$), there was no association between positive peritoneal cytology and recurrence (Figure 4A).

Positive peritoneal cytology in ADC-type cervical cancer was associated with a significant increase in lymph node metastasis (OR: 2.435; 95% CI: 1.088–5.450; $P=0.030$ and $I^2=0\%$). Positive peritoneal cytology in cervical cancer with ADC plus SCC histological type was also associated with lymph node metastasis (OR: 7.024; 95% CI: 2.422–20.368; $P<0.001$ and $I^2=0\%$). As for the SCC histological type, there were two studies (OR: 4.224; 95% CI: 1.343–13.288; $P=0.014$ and $I^2=0\%$) (Figure 4B) (Delgado *et al*, 1989; Kashimura *et al*, 1997).

These results suggest that positive peritoneal cytology is associated with a higher risk of recurrence, especially for the ADC or adenosquamous carcinoma histological types, and with higher rates of lymph node metastasis, regardless of histological type.

Publication bias. A funnel plot for publication bias was slightly asymmetric (Figure 5A). This asymmetry could be caused by small study effects. The Begg and Mazumdar rank correlation test showed no significance ($P=0.296$). The Begg's test presents some important limitations. A significant correlation suggests that a bias exists, but does not directly address the implications of this bias. Conversely, a non-significant correlation may be due to low statistical power, and cannot be considered as evidence that bias is absent. In this study, the Egger's test showed significance ($P=0.038$). The classic fail-safe N -method can address the concerns that the entire observed effect may be an artefact of bias. This meta-analysis incorporates data from three studies, which yielded a z -value of 4.64 and a corresponding two-tailed P -value of 0.00001. The fail-safe N is 14. This means that we would need to locate and include 14 'null' studies in order for the combined two-tailed P -value to exceed 0.050. However, a funnel plot for publication bias regarding LN metastasis was almost symmetric (Figure 5B).

Table 1. Characteristics of studies included in the meta-analysis

Study year	Study period/country	Mean age (years)	FIGO stage	Histological type	Median follow-up period (months)	Peritoneal cytology	Sample size	Recurrence	LN metastasis	Adjusted variables
Kuji et al, 2014	Japan/2002–2010	49.3 (20–75)	1B (179) 2A (25) 2B (24)	SCC (139) ADC (76) ASC (13)	51 (4–115)	Positive	Total (9)	SCC (1) ADC + ASC (5) Total (6)	Total (6)	Peritoneal cytology, histological type, LN metastasis, LVSI, parametrium invasion, deep stromal invasion, uterine body invasion, ovarian metastasis
						Negative	Total (219)	ADC + ASC (11)	Total (51)	
Kasamatsu et al, 2009	Japan/1984–2003	48	1B–2B	ADC (107)	72 (1–281)	Positive	ADC (16)	ADC (8)	ADC (5)	Peritoneal cytology, LN metastasis, LVSI, tumour size, depth in cervical wall, parametrium invasion, infiltration to vaginal, ovarian metastasis, histological grade
						Negative	ADC (91)	ADC (16)	ADC (17)	
Takeshima et al, 1997	Japan/1982–1993	NM	1B–2B	SCC ADC ASC	(36–168)	Positive	SCC (4) ADC + ASC (15) Total (19)	SCC (1) ADC + ASC (7) Total (8)	ADC + ASC (7)	Age, peritoneal cytology, LN metastasis, vessel permeation, muscle invasion, ovarian metastasis, parametrial invasion, stage
						Negative	SCC (238) ADC + ASC (117) Total (355)	SCC (39) ADC + ASC (27) Total (66)	ADC + ASC (27)	
Kashimura et al, 1997	Japan/1978–1994	NM	1B–2B	SCC ADC	NM	Positive	SCC (12) ADC (10) Total (22)	NR	SCC (8) ADC (7) Total (15)	Age, histology, LN metastasis, para-aortic LN metastasis, ovarian metastasis, peritoneal cytology
						Negative	SCC (215) ADC (49) Total (264)	NR	SCC (59) ADC (13) Total (72)	
Ito and Noda, 1992	Japan/1978–1994	(34–77)	2	SCC ADC ASC	(0–70)	Positive	Total (10)	Total (4)	Total (8)	
						Negative	Total (93)	Total (6)	Total (32)	
Delgado et al, 1989	US/1981–1984	NM	1	SCC	NM	Positive	SCC (2)	NR	SCC (0)	Age, LVSI, depth of invasion, parametrial invasion
						Negative	SCC (625)	NR	SCC (97)	

Abbreviations: ADC = adenocarcinoma; ASC = adenosquamous carcinoma; FIGO = International Federation of Gynecology and Obstetrics; LN = lymph node; LVSI = lymphovascular space invasion; NM = not mentioned; NR = not reported; SCC = squamous cell carcinoma.

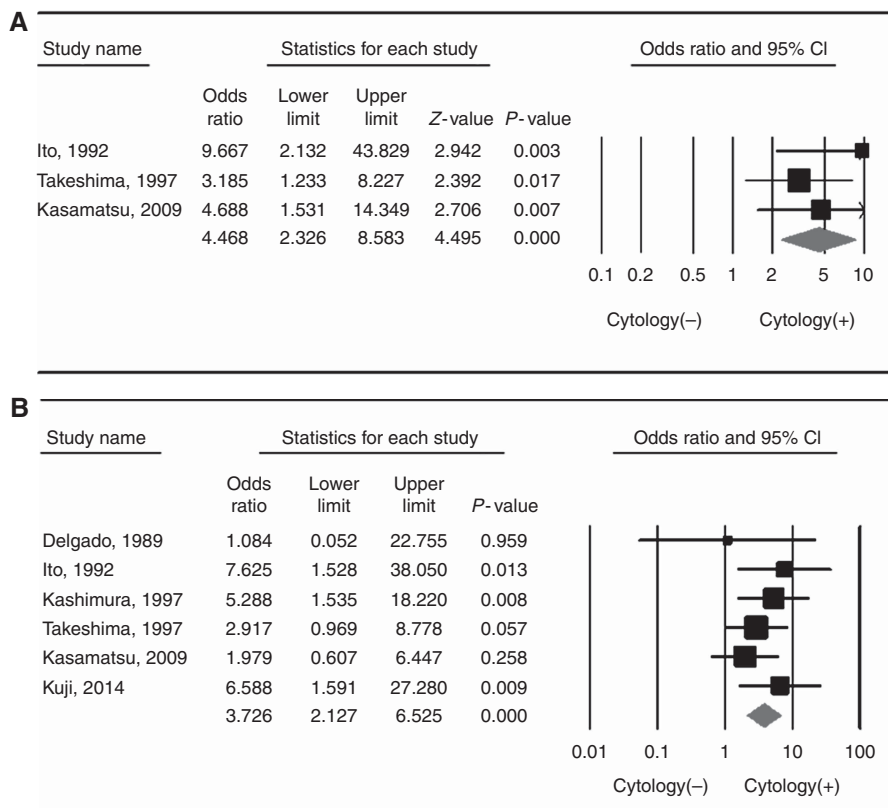


Figure 2. The odds ratio for the risk of (A) recurrence and (B) LN metastasis for each study and all studies combined comparing positive peritoneal cytology with negative cytology in a meta-analysis based on the fixed-effects model. Heterogeneity was low across studies (A: $P=0.473$ and $I^2=0\%$; B: $P=0.606$ and $I^2=0\%$). The size of each square is proportional to the sample size for each study, and the horizontal line through the square indicates the 95% confidence interval for that study. For the pooled analysis, the diamond indicates the pooled value, and the right and left ends of the diamond indicate the 95% confidence interval for the analysis.

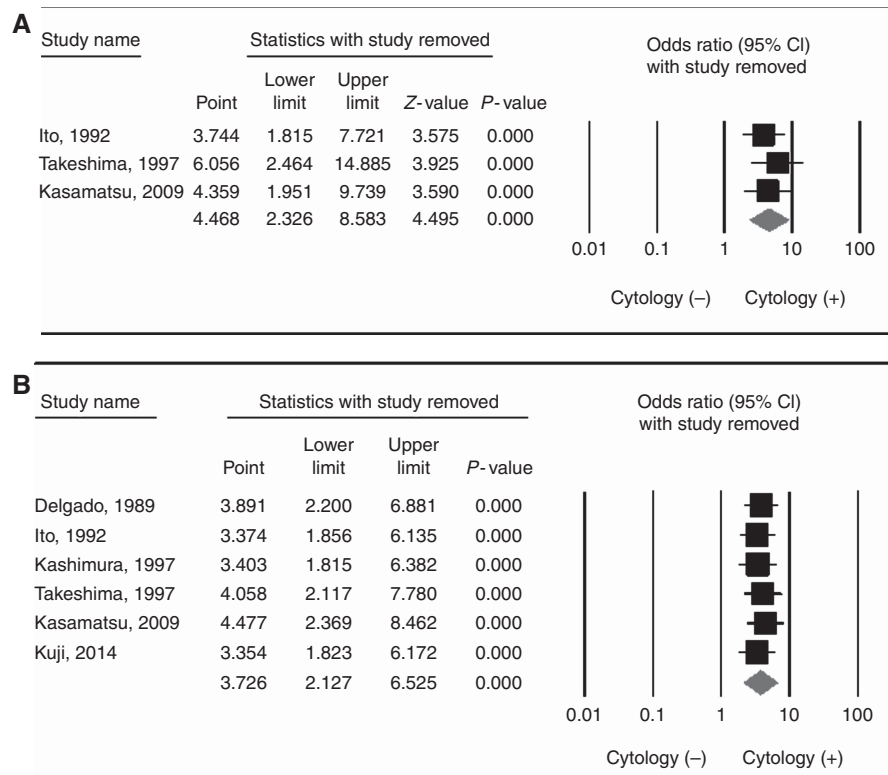
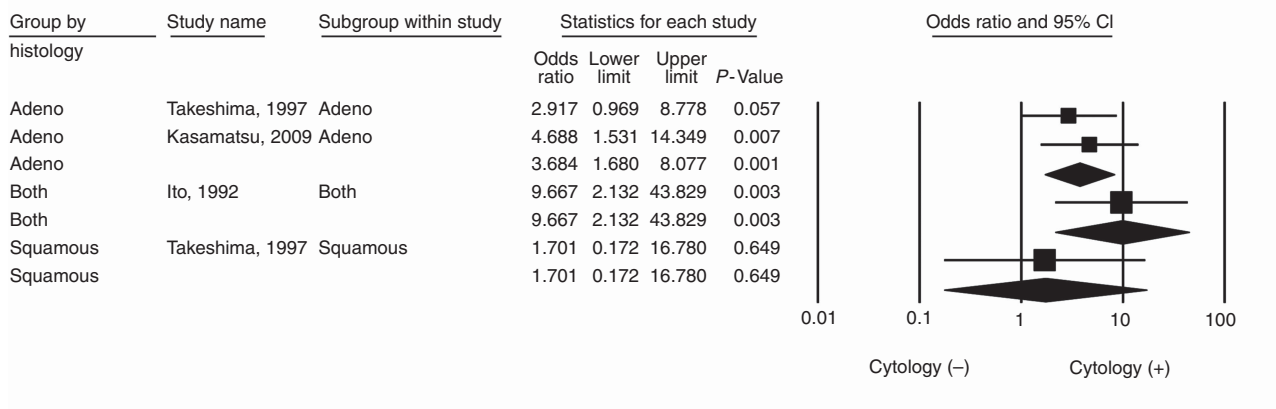


Figure 3. Sensitivity analysis of the summary odds ratio coefficients on the relationships between abnormal peritoneal cytology and prognosis (A: recurrences, B: LN metastasis) of patients with cervical cancer.

A



B

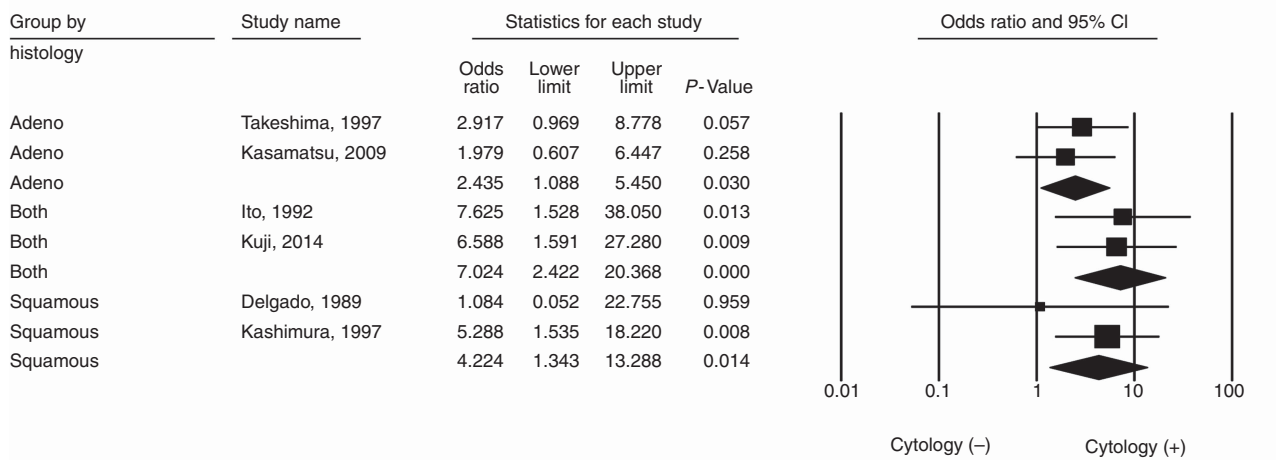


Figure 4. Positive peritoneal cytology and the risk of (A) recurrence and (B) LN metastasis in the subgroup meta-analysis by histological type, based on the fixed-effects model.

DISCUSSION

According to published data, patients with positive peritoneal cytology had poorer prognostic outcomes, such as survival rates and recurrence, than those with negative cytology. However, the sample size in most studies was not large enough to sufficiently explain the effectiveness of cytology on cervical cancer prognosis, and no quantitative analysis has estimated the efficacy of cytology on cervical cancer prognosis. Moreover, it is well known that, positive peritoneal cytology overlaps with other risk factors. Roberts *et al* (1986) reported that positive peritoneal cytology was associated with a very poor prognosis, and it was also associated with other poor prognostic factors (Roberts *et al*, 1986). Thus, no consensus was reached as to whether positive peritoneal cytology is an independent risk factor. Takeshima *et al* (1997) found that peritoneal cytology was not a prognostic factor for stage I and II ADC, although cardinal ligament invasion, lymph node metastases, and muscle layer invasion were prognostic factors (Takeshima *et al*, 1997). Kasamatsu *et al* (2009) found that peritoneal cytology, para-aortic lymph nodes, and pelvic lymph nodes were independent prognostic factors, irrespective of the histological type (Kasamatsu *et al*, 2009). Kuji *et al* (2014) reported that positive peritoneal cytology may be associated with a poor prognosis in adenosquamous carcinoma or ADC of cervix (Kuji *et al*, 2014). The results of the present meta-analysis indicate that

positive peritoneal cytology of cervical cancer patients leads to a significant increase in the risk of cervical cancer recurrence. However, the results of the subgroup analysis based on the histology show slightly different patterns. The estimates from the ADC histology type indicate that positive peritoneal cytology leads to an increase in the risk of recurrence (OR: 3.684; 95% CI: 1.680–8.077; $P=0.001$), whereas those from the squamous cell type did not lead to a significant increase in the risk of recurrence (OR: 1.701; 95% CI: 0.172–16.780; $P=0.649$). This finding might suggest the possibility that positive peritoneal cytology increases disease recurrence by the spread of viable tumour cells. If we can conclude that positive peritoneal cytology, particularly for patients with ADC, leads to recurrence by peritoneal dissemination through hematogenous or lymphatic spread, then positive peritoneal cytology would indicate systemic disease. According to the qualitative analysis, positive results of peritoneal cytology seem to be associated with high recurrence rates through peritoneal dissemination. The authors reported that the incidence of peritoneal spread at the first recurrence in the positive cytology group (62.5%) was significantly higher than that in the negative cytology group (12.5%) (Kasamatsu *et al*, 2009). In addition, another study reported that peritoneal recurrence of ADC among patients with positive peritoneal cytology occurred in 60% of cases (Kuji *et al*, 2014). This percentage tended to be higher than that in patients with negative cytology. However, in the present meta-analysis, we could not conduct a quantitative meta-analysis on the

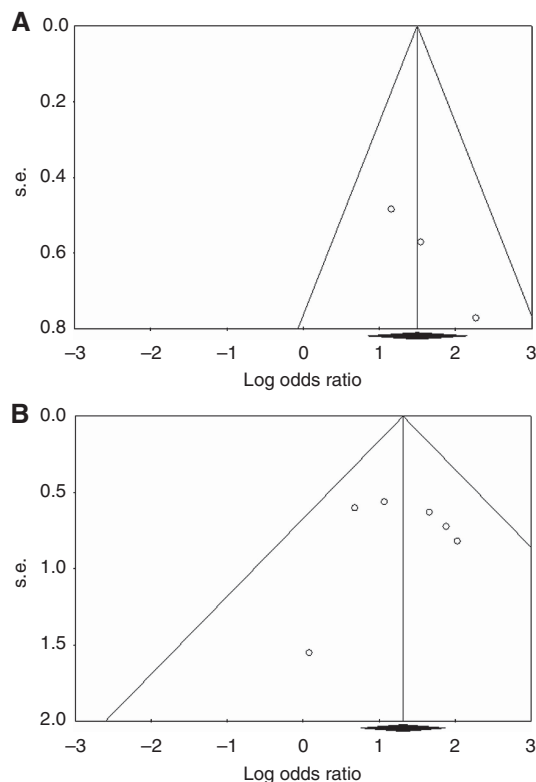


Figure 5. Assessment of publication bias using funnel plot analysis. (A) Funnel plot analysis of studies on recurrence. The funnel plot has an asymmetrical distribution, suggesting the presence of selection bias. (B) Funnel plot analysis of studies on LN metastasis. The Funnel plot has an almost symmetrical distribution. Publication bias was not found in the meta-analysis of LN metastasis.

relationship between abnormal peritoneal cytology and metastatic pattern including peritoneal dissemination, because we could not obtain detailed individual data. Considering the above facts, further investigation and well-designed randomised controlled trials may be needed to reach a definitive conclusion.

Delgado *et al* (1989) found that the factors identified as independent risk factors for pelvic lymph node metastasis by multivariate analysis were depth of invasion, parametrium involvement, lymph-vascular space involvement, and age, but not peritoneal cytology (Delgado *et al*, 1989). Moreover, Ito and Noda (1992) reported that negative cytology was often found even in cases with metastasis to retroperitoneal lymph nodes, whereas positive cytology was found in cases without metastasis (Ito and Noda, 1992). These authors suggested that the mechanism of cervical carcinoma metastasis to retroperitoneal lymph nodes might not be the same as that of spreading into the abdominal cavity. However, Kashimura *et al* (1997) reported that peritoneal cytology, lymph node metastasis, ovarian metastasis, and histological grade are independent prognostic factors in stage I and stage II ADC of the cervix (Kashimura *et al*, 1997). The results of our meta-analysis indicate that positive peritoneal cytology of cervical cancer patients leads to a significant increase in the risk of lymph node metastasis. This pattern was also observed in the subgroup analysis for histological type. The estimates from the ADC histology type and SCC type indicate that positive peritoneal cytology leads to an increase in the risk of lymph node metastasis (OR: 2.435; 95% CI: 1.088–5.450; $P=0.030$, and OR: 4.224; 95% CI: 1.343–13.288; $P=0.014$, respectively). This finding could present, whatever histology type of cancer was, significant increase in lymph node metastasis was found between the peritoneal cytology positive and cytology negative groups.

Our meta-analysis results revealed that positive peritoneal cytology was associated with recurrence in histology type including ADC or adenosquamous carcinoma and lymph node metastasis regardless of histological type. Therefore, it is crucial to obtain peritoneal cytology fluid routinely at the time of operation in patients with early-stage cervical cancer, especially ADC histological type. Although we performed adjuvant treatment such as postoperative concurrent chemoradiotherapy or radiotherapy according to the risk factors, if positive peritoneal cytology truly reflects peritoneal spread or affects survival adversely, we think that systemic chemotherapy could be considered as the treatment of choice for patients with positive peritoneal cytology, especially for those with the ADC histological type, for similar reasons regarding peritoneal cytology as a risk factor of endometrial and ovarian cancers (Rahaman *et al*, 2009; Berek, 2012a,b). Patients with positive cytology along with poor prognostic factors may potentially benefit from systemic chemotherapy in endometrial cancer (Berek, 2012b).

Nevertheless, several limitations of the present meta-analysis should be recognised. First, as our meta-analysis was a retrospective study, it may have led to subject selection bias, which could have influenced the reliability of our results. Second, this meta-analysis was based on data published from the included studies, and we could not obtain detailed individual data. Thus, we were not able to correct all clinicopathological parameters into a consistent standard, for example, stage, risk factors (lymph node status, parametrial invasion, operative margin status, tumour size, lymphovascular space invasion, and deep stromal invasion), treatment method (e.g., radical operation field scale or adjuvant treatment method), follow-up period, recurrence diagnostic method, and recurrent pattern. Therefore, it was not possible to perform multivariate analysis and to determine the independent associated risk factor of poor prognosis among patients with positive peritoneal cytology and lymph node involvement in the present meta-analysis. In addition, we could not control potentially relevant bias factors (i.e., age, and ethnic group). Finally, funnel plot analyses concerning publication bias were also performed to confirm the reliability of our research results. In our meta-analysis, the publication bias in positive peritoneal cytology with recurrence may exist, but not with lymph node metastasis in cervical cancer. Consequently, more studies should be performed so that they can be included in a meta-analysis.

Although our study has some limitations, we believed it is the first meta-analysis focusing on the relationships between peritoneal cytology and the prognosis of cervical cancer. Furthermore, we made an effort to perform a highly sensitive literature search strategy utilising electronic databases.

In summary, to our knowledge, our meta-analysis is the first report to show that positive peritoneal cytology may be strongly associated with poor prognosis in cervical cancer. Our meta-analysis indicates that peritoneal cytology may serve as a prognostic factor for cervical cancer. Thus, it is essential to obtain peritoneal cytology routinely at the time of laparotomy in patients with cervical cancer about histology type including ADC or adenosquamous carcinoma, especially. Moreover, the results of peritoneal cytology must be considered in postoperative treatment planning. Therefore, we propose that positive cytology should be reported separately without changing the stage, and suggest that positive peritoneal cytology is a risk factor that should be taken into account when making decisions concerning postoperative adjuvant therapy in patients with early-stage cervical cancer. When the result of peritoneal cytology is positive, additional aggressive postoperative chemotherapy may be proposed as an adjuvant therapy.

However, owing to the limitations acknowledged above, further research, with larger sample sizes and more amount of comprehensive data, is still required to provide a more representative statistical analysis. Therefore, well-designed randomised controlled trials or prospective cohort studies are needed in the future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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