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 survival curves; (5) the follow-up period was clearly documented; and, thus, were included in the meta-analysis (Delgado et al., 1989; Zuna et al., 2009; Kuji et al., 2014).

Data extraction. 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 I², which measures the percentage of the total variation across studies. Here substantial heterogeneity was defined as an I²-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.

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 I², which measures the percentage of the total variation across studies. Here substantial heterogeneity was defined as an I²-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 Borach, 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 (Cresman and Rutledge, 1971; Keetel 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 (Cresman 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 (Keetel 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-IIB disease. Most histologic types, in particular, SCC, ADC and adenosquamous
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 ($I^2 = 0$%), 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) | Peritoneal cytology, histological type, LN metastasis, LVSI, parametrium invasion, deep stromal invasion, uterine body invasion, ovarian metastasis |
| 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 |
| 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, parametral invasion, stage |
| 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 |
| Ito and Noda, 1992 | Japan/1978–1994 | (34–77) | 2 | SCC ADC ASC | (0–70) | Positive | Total (10) | Total (4) | Total (8) | Age, LVSI, depth of invasion, parametral invasion |
| Delgado et al, 1989 | US/1981–1984 | NM | 1 | SCC | NM | Positive | SCC (2) | NR | SCC (0) | |

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.
that positive peritoneal cytology may be associated with a poor prognosis. 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 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. 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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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