Clinicopathological significance of survivin expression in patients with cervical cancer: A systematic meta-analysis

Yibing Fan\textsuperscript{a} and Juan Chen\textsuperscript{b}

\textsuperscript{a}Department of Obstetrics and Gynecology, The Fifth Clinical Medical College of Yangzhou University, the Second People’s Hospital of Obstetrics and Gynecology of Changshu City, Changshu, China; \textsuperscript{b}Department of Gynecology, GongLi Hospital Affiliated of the Second Military Medical University, Shanghai, China

\textbf{ABSTRACT}
Survivin has been shown to play an important role in cancer pathogenesis. However, its role in cervical cancer development is still controversial. This study was performed to evaluate the clinical significance of survivin expression in cervical cancer. A search of some online electronic databases was conducted to identify available studies. The pooled odds ratios (ORs) with its 95% confidence intervals (CIs) were calculated and analyzed. Finally, 18 eligible studies with 791 cervical cancer patients, 1,013 cervical intraepithelial neoplasia (CIN) lesions, 199 normal cervical tissues, and 95 samples with chronic cervicitis were identified in this analysis. The pooled OR of survivin expression was found to be significantly higher in the samples from cervical cancer than in those from CIN lesions, normal cervical tissues, and chronic cervicitis. When cervical cancer was compared to CIN lesions, the subgroup analysis by ethnicity showed that survivin expression was associated with a risk of cervical cancer in Asians ($P < 0.001$), but not in Caucasians ($P = 0.659$). In addition, survivin was significantly more overexpressed in high-grade cervical cancer than in low-grade cervical cancer. Its expression was also more elevated in advanced-stage patients than in early-stage patients, in lymph node metastasis than in lymph node without metastasis, and in squamous cell carcinoma (SCC) than in adenocarcinoma (AC). The expression of survivin may play a key role in the carcinogenesis, progression, and metastasis of cervical cancer. However, survivin expression may be involved in the progression of CIN lesions only in the Asian population. Survivin expression is associated with an increased risk of SCC. Additional studies with larger sample sizes are needed in the future to confirm our findings.

\textbf{KEYWORDS}
cervical cancer; CIN lesions; clinicopathological features; expression; survivin protein

\textbf{Introduction}
Cervical cancer is the most common malignant gynecologic disease and the most lethal gynecologic carcinoma. According to the global cancer statistics, approximately 527,600 new cases of cervical cancer were clinically diagnosed in 2012, leading to an estimated 265,700 deaths due to cervical cancer in the world.\textsuperscript{1} Cervical cancer includes 2 main histological subtypes: squamous cell carcinoma (SCC), comprising 85%–90% of the cases, and adenocarcinoma (AC), constituting 10%–25%.\textsuperscript{2} In recent decades, surgery and radiotherapy have been the main modalities for the management of cervical cancer, but no considerable advancements in their therapeutic efficiency have been observed, and the 5-year survival rate remains poor. In addition, at the time of diagnosis, most patients with cervical carcinoma have overt invasiveness and metastasis.\textsuperscript{3-5} Therefore, the uncontrolled local tumor progression and the distant spread of metastases are still the main causes of death in cervical cancer patients.

Apoptosis is a mechanism that is crucially important for the preservation of tissue homeostasis and morphogenesis. The suppression of apoptosis is related to increased carcinogenesis through aberrantly mediating cell survival or the enhanced accumulation of transforming mutations. The Bcl-2 family and the inhibitor of apoptosis protein (IAP) family are 2 major regulators of apoptosis.\textsuperscript{6-8} The survivin gene, mapped to human chromosome 17q25, encodes the survivin protein, also called baculoviral inhibitor of apoptosis...
repeat-containing-5 (BIRC5), that is a member of IAP family. Survivin expression is considered to be associated with cell proliferation, angiogenesis, and inhibition of apoptosis. Some studies have shown that the expression of survivin may be considered as a prospective novel anticancer therapeutic target in various cancers. In addition, biosensor methods have recently been developed for testing of survivin expression trough the detection of survivin mRNA or survivin protein.

Although numerous studies during recent decades have reported an association between survivin expression levels and cervical cancer, the results remain controversial. Therefore, to evaluate the effect of survivin expression on cervical cancer development, we performed this meta-analysis based on the findings of all published articles.

Materials and methods

Search strategy

The online electronic databases (PubMed, EMBASE, EBSCO, and Cochrane Library) were carefully searched prior to August 11th, 2016 using the following keywords and search terms: (uterine cervix OR cervical) AND (cancer OR carcinoma OR tumor OR neoplasm) AND (survivin OR BIRC5 OR baculoviral inhibitor of apoptosis repeat-containing 5 OR baculoviral IAP repeat containing 5). Furthermore, we manually searched the reference lists of available studies to obtain other potential articles.

Inclusion criteria

Eligible studies were included based on the following inclusion criteria: (1) the patients were diagnosed with cervical cancer based on histopathological examination; (2) studies of tissue samples using immunohistochemistry (IHC) with a case-control or cohort design; (3) the studies provided sufficient data on the frequency of survivin expression to evaluate the relationship between survivin expression and cervical cancer in cancer vs. control groups; (4) the studies had sufficient data to evaluate the correlation of survivin expression with the clinicopathological characteristics of cervical cancer; (5) when multiple publications reported data from overlapping samples, the study reporting the largest set of sample data was selected in this meta-analysis; (6) studies published in English were included.

Data extraction

Based on a predefined form, 2 investigators independently extracted relevant information from eligible studies. Discrepancies on data extraction were discussed with the authors. The following data were included: surname of the first author, year of publication, country, and ethnicity of the studied population, as well as sample size, expression frequency, and clinicopathological features, such as tumor grade, clinical stage, histopathological subtype, and lymph node status. Tumors of grades 1–2 were defined as low-grade, and tumors of grade 3 were defined as high-grade. Tumor stages 1–2 were referred to as early stage and tumor stages 3–4 as advanced stage. The control groups included samples from normal cervical tissue, chronic cervicitis, and cervical intraepithelial neoplasia (CIN) lesions.

Statistical analysis

All statistical analyses were conducted using Stata 12.0 software (StatCorp, College Station, TX, USA). The pooled odds ratio (OR) and the corresponding 95% confidence interval (95% CI) were analyzed to evaluate the correlation between survivin expression and cervical cancer in cancer vs. normal cervical tissues, chronic cervicitis, and cervical intraepithelial neoplasia (CIN) lesions. In addition, the pooled OR and the corresponding 95% CI were also calculated to determine whether survivin expression was associated with clinicopathological characteristics, including tumor grade, clinical stage, histopathological subtype, and lymph node status. A statistical test for heterogeneity was conducted using the chi-square test and Q statistic. In the cases of substantial heterogeneity among studies ($I^2 > 50\%$ or $p < 0.1$), a random-effects model was applied. Moreover, meta-regression and subgroup analyses were used to further assess the possible sources of heterogeneity. Otherwise, a fixed-effects model was used in this study, indicating a lack of heterogeneity. A sensitivity analysis was also performed to evaluate the stability of the results and the influence of deleting an individual study. The potential publication bias was identified using Egger’s linear regression test. A $P$-value of less than 0.05 was regarded as statistically significant.
Results

Study characteristics

A total of 692 potential articles were initially retrieved through the database searches. According to the above inclusion criteria, the frequencies of survivin protein expression in cervical cancer were evaluated in 18 studies (Fig. 1). Among these studies, 16 studies evaluated the relationship between survivin expression and cervical cancer in cancer vs. CIN lesions, including 732 cervical cancer patients and 1013 CIN lesions. In addition, 13 studies assessed the correlation between survivin expression and cervical cancer in cancer vs. normal cervical tissues, including 664 patients with cervical cancer and 199 normal cervical tissue samples. Further, 5 studies examined the association between survivin expression and cervical cancer in cancer vs. chronic cervicitis, including 210 cervical cancer patients and 95 samples with chronic cervicitis, and 8 studies involving 413 patients with cervical cancer analyzed the association of survivin expression with tumor grade in cervical cancer. Eight studies with 409 cervical cancer patients with investigated the association of survivin expression with tumor stage; 7 studies involving 357 patients with cervical cancer assessed the association of survivin expression with tumor histology in cervical cancer. Additionally, 7 studies enrolling 401 patients with cervical cancer estimated the association of survivin expression with lymph node status in cervical cancer.

Correlation between survivin expression and cervical cancer in cancer vs. controls

In the comparison between cervical cancer and control groups, the random-effects model was used in the current study. As can be seen in Fig. 2, survivin expression was notably higher in cervical cancer than in CIN lesions, normal cervical tissues, and chronic cervicitis (OR = 3.01, 95% CI = 1.60–5.68, P = 0.001; OR = 51.72, 95% CI = 22.83–117.20, P < 0.001; OR = 26.55, 95% CI = 7.20–97.95, P < 0.001; respectively), indicating that survivin expression was significantly associated with an increased risk of cervical cancer.

Subgroup analyses of survivin expression in cancer vs. controls

Subgroup analyses by ethnicity (Asians and Caucasians) and expression location (cytoplasm and cytoplasm/nucleus) were conducted to find the association in different subgroups (Table 2). The subgroup analysis based on ethnicity comparing cervical cancer with CIN lesions revealed that survivin expression was correlated with cervical cancer in the Asian population (OR = 3.61, 95% CI = 1.94–6.71, P < 0.001), but not in the Caucasian population (OR = 1.64, 95% CI = 0.18–14.85, P = 0.659). The subgroup analysis of survivin concerning expression location indicated that survivin expression was correlated with cervical cancer.
| First author   | Country   | Ethnicity | Expression location | Cancer T (E+ %) | CIN lesions T (E+ %) | Chronic cervicitis T (E+ %) | Normal tissues T (E+ %) | Grade 3 E+/T | Grade 1–2 E+/T | Stage 3–4 E+/T | SCC E+/T | AC E+/T | N+: E+/T | N– E+/T | IHC Cut off (positivity) |
|---------------|-----------|-----------|---------------------|-----------------|---------------------|-----------------|-----------------|-------------|-------------|---------------|----------|--------|---------|--------|---------------------|
| Kim 2002 [17] | Korea     | Asians    | C/N                 | 13 (100)        | 28 (78.6)          | 5 (0)           |                 |             |             |               |          |        |         |        | >5% focal or diffuse |
| Frost 2002 [16]| USA       | Caucasians| C                   | 10 (40)         | 32 (71.9)          |                 |                 |             |             |               |          |        |         |        | >5% focal or diffuse |
| Singh 2004 [38]| India     | Caucasians| C/N                 | 50 (48)         |                    |                 |                 |             |             |               |          |        |         |        | >20% weak-strong    |
| Lee 2005 [37] | Korea     | Asians    | C/N                 | 53 (96.2)       | 14 (71.4)          |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Branca 2005 [36]| Italy   | Caucasians| C/N                 | 143 (99.3)      | 134 (89.6)         |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Lu 2005 [35]  | China     | Asians    | C                   | 41 (78)         | 17 (47.1)          |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Mu 2007 [34]  | China     | Asians    | C                   | 50 (90)         | 128 (53.1)         |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Lee 2005 [37] | Korea     | Asians    | C/N                 | 53 (96.2)       | 14 (71.4)          |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Kim 2002 [17] | Korea     | Asians    | C/N                 | 13 (100)        | 28 (78.6)          | 5 (0)           |                 |             |             |               |          |        |         |        | >5% focal or diffuse |
| Frost 2002 [16]| USA       | Caucasians| C                   | 10 (40)         | 32 (71.9)          |                 |                 |             |             |               |          |        |         |        | >5% focal or diffuse |
| Singh 2004 [38]| India     | Caucasians| C/N                 | 50 (48)         |                    |                 |                 |             |             |               |          |        |         |        | >20% weak-strong    |
| Lee 2005 [37] | Korea     | Asians    | C/N                 | 53 (96.2)       | 14 (71.4)          |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Branca 2005 [36]| Italy   | Caucasians| C/N                 | 143 (99.3)      | 134 (89.6)         |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Lu 2005 [35]  | China     | Asians    | C                   | 41 (78)         | 17 (47.1)          |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Mu 2007 [34]  | China     | Asians    | C                   | 50 (90)         | 128 (53.1)         |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Lee 2005 [37] | Korea     | Asians    | C/N                 | 53 (96.2)       | 14 (71.4)          |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Kim 2002 [17] | Korea     | Asians    | C/N                 | 13 (100)        | 28 (78.6)          | 5 (0)           |                 |             |             |               |          |        |         |        | >5% focal or diffuse |
| Frost 2002 [16]| USA       | Caucasians| C                   | 10 (40)         | 32 (71.9)          |                 |                 |             |             |               |          |        |         |        | >5% focal or diffuse |
| Singh 2004 [38]| India     | Caucasians| C/N                 | 50 (48)         |                    |                 |                 |             |             |               |          |        |         |        | >20% weak-strong    |
| Lee 2005 [37] | Korea     | Asians    | C/N                 | 53 (96.2)       | 14 (71.4)          |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Branca 2005 [36]| Italy   | Caucasians| C/N                 | 143 (99.3)      | 134 (89.6)         |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Lu 2005 [35]  | China     | Asians    | C                   | 41 (78)         | 17 (47.1)          |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |
| Mu 2007 [34]  | China     | Asians    | C                   | 50 (90)         | 128 (53.1)         |                 |                 |             |             |               |          |        |         |        | >5% weak-heavy      |

C: cytoplasm; N: nucleus; E+: survivin expression positive status; T: number of tissue samples; IHC: immunohistochemistry method; CIN: cervical intraepithelial neoplasia; SCC: squamous cell carcinoma; AC: adenocarcinoma; N+: lymph node positive status; N–: lymph node negative status.
in the cytoplasm and in the cytoplasm/nucleus (OR = 3.29, 95% CI = 1.62–6.66, P = 0.001; OR = 3.14, 95% CI = 1.01–9.80, P = 0.049).

The comparison between samples from cervical cancer and normal cervical tissues in the subgroup analysis based on ethnicity showed that survivin expression was associated with cervical cancer in the ethnic subgroups investigated (Asians: OR = 41.29, 95% CI = 10.62–159.73, P < 0.001; OR = 64.00, 95% CI = 21.44–91.10, P < 0.001). The comparison of cancer and chronic cervicitis, the subgroup analysis by survivin expression location indicated that survivin expression was correlated with cervical cancer in both locations, the cytoplasm and the cytoplasm/nucleus (OR = 41.20, 95% CI = 10.62–159.73, P < 0.001; OR = 4.20–169.65, P = 0.001; OR = 38.11, 95% CI = 2.57–564.83, P = 0.008).

### Figure 2. Forest plot of the correlation between survivin expression and cervical cancer in 16 studies with 732 cervical cancer patients and 1,013 CIN lesions: OR = 3.01, 95% CI = 1.60–5.68, P = 0.001, 13 studies with 664 patients with cervical cancer and 199 normal cervical tissues: OR = 51.72, 95% CI = 22.83–117.20, P < 0.001, 5 studies with 210 cervical cancer patients and 95 samples with chronic cervicitis: OR = 26.55, 95% CI = 7.20–97.95, P < 0.001.

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| Normal   |             |          |
| Singh 2004 | 37.91 (2.17, 661.02) | 2.17 |
| Lee 2005  | 14.57 (2.24, 84.75) | 3.04 |
| Branca 2005 | 1805.00 (68.78, 47363.64) | 1.89 |
| Mu 2007  | 8.30 (1.78, 38.76) | 3.36 |
| Tan 2010  | 216.00 (23.88, 1598.13) | 2.72 |
| Bai 2013  | 1001.00 (89.22, 26218.32) | 1.89 |
| Wu 2012  | 27.00 (1.04, 668.79) | 1.90 |
| Lu 2012  | 85.97 (4.87, 1516.07) | 2.17 |
| Kim 2014  | 22.50 (2.50, 189.51) | 2.77 |
| Liu 2015  | 22.62 (1.34, 418.09) | 2.14 |
| Zhou 2015  | 56.00 (11.38, 275.47) | 3.31 |
| Zhou 2016  | 102.35 (3.72, 1700.86) | 2.17 |
| Subtotal (I-squared = 32.5%, p = 0.122) | 74.45 (3.74, 1481.60) | 2.06 |
| Cervicitis |             |          |
| Kim 2002  | 257.00 (2.51, 16954.38) | 1.45 |
| Wu 2012  | 12.09 (0.07, 457.97) | 3.52 |
| Cao 2014  | 541.84 (30.86, 9575.77) | 2.16 |
| Zhou 2015  | 10.50 (3.05, 36.14) | 3.65 |
| Zhou 2015  | 15.20 (2.42, 95.34) | 3.07 |
| Subtotal (I-squared = 56.1%, p = 0.058) | 28.51 (7.20, 97.95) | 19.86 |
| NOTE: Weights are from random effects analysis | | |
Altogether, our results revealed that survivin protein expression can be detected in the cytoplasm and in the cytoplasm/nucleus. However, the result from the comparison of cancer and chronic cervicitis should be cautiously interpreted as only a small number of subjects were included in this study.

**Correlation of survivin expression with clinicopathological features in cervical cancer**

Next, we determined whether survivin expression was associated with the clinicopathological characteristics of cervical cancer. The fixed-effects model was applied since no substantial heterogeneity was observed (all \( p > 0.1 \) or \( I^2 < 50\% \)). The pooled OR from 8 studies including 106 high-grade patients with cervical cancer and 307 low-grade patients with cervical cancer demonstrated that survivin expression was significantly higher in high-grade cervical cancer than in low-grade cervical cancer (OR = 2.13, 95% CI = 1.13–3.98, \( p = 0.019 \) (Fig. 3). The pooled OR from 8 studies involving 122 advanced stage patients with cervical cancer and 287 early stage patients with cervical cancer showed that survivin expression was significantly higher in advanced-stage cervical cancer than in early-stage cervical cancer (OR = 2.96, 95% CI = 1.51–5.80, \( p = 0.002 \) (Fig. 4). Furthermore, the overall OR from 7 studies including 302 squamous cell carcinoma (SCC) and 55 adenocarcinoma (AC) indicated that survivin expression in SCC was slightly higher than in AC (OR = 1.99, 95% CI = 1.02–3.88, \( p = 0.045 \) (Fig. 5). In addition, the overall OR from 7 studies involving 200 lymph node positive patients with cervical cancer and 201 lymph node negative patients with cervical cancer demonstrated that survivin expression was significantly higher in lymph node-positive cervical cancer than in lymph node-negative cervical cancer (OR = 8.20, 95% CI = 4.09–16.45, \( p < 0.001 \) (Fig. 6).

As a whole, our results revealed that survivin expression in cervical cancer was correlated with tumor grade, tumor stage, histological subtype, and lymph node status. However, the result comparing SCC and AC should be carefully considered as only 55 patients of AC were analyzed in this study.

**Meta-regression and sensitivity analyses in cancer vs. CIN lesions and chronic cervicitis**

Significant heterogeneity was found when cervical cancer was compared with CIN lesions and chronic cervicitis (\( p < 0.1 \) or \( I^2 > 50\% \)). Thus, meta-regression and sensitivity analyses were carried out in the current study. The former were performed to find the possible sources of heterogeneity in survivin expression (Table 3). Based on ethnicity (Asians and Caucasians) and expression location (cytoplasm and cytoplasm/nucleus), meta-regression analysis could not explain the heterogeneity in the comparison of cancer and CIN lesions (\( p > 0.05 \). The result of the meta-regression analysis of survivin expression by expression location (cytoplasm and cytoplasm/nucleus) could not reveal the potential source of heterogeneity in the comparison of cancer and chronic cervicitis (\( P = 0.864 \).

To estimate the stability of the combined OR and the change of heterogeneity, sensitivity analyses were

| Subgroup/n | Pooled OR (95 % CI) | \( I^2; p \) | \( P \) | Cases | Controls | Compared groups |
|-----------|---------------------|-------------|---------|-------|----------|-----------------|
| Race      |                     |             |         |       |          |                 |
| Asians/12 | 3.61 (1.94–6.71)    | 71.8%; < 0.001 | <0.001  | 556   | 732      | Cancer vs. CIN lesions |
| Caucasians/4 | 1.64 (0.18–14.85) | 81.5%; 0.001 | 0.659  | 176   | 281      |                 |
| Expression location |          |             |         |       |          |                 |
| C/N/9     | 3.14 (1.01–9.80)    | 79.7%; < 0.001 | 0.049  | 409   | 665      |                 |
| C/7       | 3.29 (1.62–6.66)    | 69.6%; 0.003 | 0.001  | 323   | 348      |                 |
| Race      |                     |             |         |       |          |                 |
| Asians/11 | 41.29 (18.78–90.81) | 21.6%; 0.238 | <0.001  | 471   | 170      | Cancer vs. Normal cervical tissues |
| Caucasians/2 | 244.02 (3.78–15771.67) | 72.9%; 0.055 | 0.01   | 193   | 29       |                 |
| Expression location |          |             |         |       |          |                 |
| C/N/8     | 64.00 (21.44–91.10) | 30.1%; 0.188 | <0.001  | 432   | 109      |                 |
| C/5       | 41.20 (10.62–159.73) | 45.3%; 0.120 | <0.001  | 232   | 90       |                 |
| Expression location |          |             |         |       |          |                 |
| C/N/2     | 38.11 (2.57–564.83) | 42.0%; 0.189 | 0.008   | 37    | 15       | Cancer vs. chronic cervicitis |
| C/3       | 26.68 (4.20–169.65) | 72.8%; 0.025 | 0.001   | 173   | 80       |                 |

C: cytoplasm; N: nucleus; CIN: cervical intraepithelial neoplasia; OR: odds ratio; 95% CI: 95% confidence intervals.
performed according to data obtained after the omission of a single study (Fig. 7). When cervical cancer was compared to CIN lesions, we removed these studies, including Kim 2014 et al., Korea, Frost 2002 et al., USA, Zhou 2015 et al., China and Barbosa 2011 et al., Brazil, and re-calculated the pooled result from the remaining 12 studies, the overall OR were 5.94 (95% CI: 4.30–8.19). In addition, heterogeneity was dramatically reduced ($p = 0.253$ and $I^2 = 19.4\%$).

When cervical cancer was compared to chronic cervicitis, we removed a study conducted in China by Cao et al., and re-calculated the result from the remaining 4 studies, and found that the pooled OR were 13.79 (95% CI: 6.26–30.34), with the absence of heterogeneity ($p = 0.485$ and $I^2 = 0.0\%$). The pooled ORs were not significantly changed, indicating that the results of our analyses were stable and credible.

**Publication bias**

Egger’s test was carried out to estimate the potential publication bias. Slight publication bias was detected in cancer vs. normal cervical tissues and chronic cervicitis, and in relation to histological subtype in cancer ($P < 0.05$) (Table S1). There was no obvious evidence of publication bias in cancer vs. CIN lesions, and in relation to tumor grade, tumor stage, and lymph node status ($P > 0.05$) (Table S1).

**Discussion**

The screening of cervical intraepithelial neoplasia (CIN) using cytological smear has decreased the morbidity and mortality of cervical cancer. Reportedly, survivin is overexpressed in cervical cancer and is considered an important factor for disease progression and spread of metastasis. However, the results regarding survivin expression frequencies in cervical cancer are still controversial and inconsistent. Moreover, the different expression levels of survivin in cervical cancer have been reported within a range from 40% to 100%.

It is noteworthy that varying expression rates of survivin were found in cases with CIN lesions, with a range from 36% to 92.6%. In addition, 4 studies reported an expression frequency of survivin in
cervical cancer that was lower than that in CIN lesions. The remaining 12 studies included in our analysis reported that survivin expression frequency was higher in cervical cancer than in CIN lesions. Evidence indicates that survivin is expressed in almost all types of human malignancies, but is rarely detected in most of the normal adult tissues. However, Lee et al. obtained results indicating a frequency of survivin expression in normal cervical tissues of 63.6%. On the other hand, Lu et al. discovered an expression frequency of survivin in normal cervical tissues of 30%. We also found that survivin expression frequencies ranged from 0% to 20% in women with chronic cervicitis. Thus, we conducted this study to evaluate the relationship between survivin expression and cervical cancer in cancer vs. control groups. Moreover, we also determined the clinical effect of survivin expression on cervical cancer.

By using immunohistochemistry (IHC), in the current study we revealed that the pooled OR of survivin expression was significantly higher in cervical cancer than in CIN lesions, normal cervical tissues, and chronic cervicitis, suggesting that survivin expression was significantly correlated with the pathogenesis of cervical cancer. The results concerning survivin expression should be interpreted with caution as the sample size were small in the comparison between cervical cancer and chronic cervicitis, which indicates the need for more studies with larger sample sizes in the future.

Subgroup analysis based on expression location revealed that the cytoplasmic and the nuclear/cytoplasmic expression of survivin were associated with cervical cancer. In the comparison between cervical cancer and CIN lesions, the subgroup analysis based on ethnicity showed that survivin expression was significantly associated with the cervical cancer risk in the Asian population (OR = 3.61, \( P < 0.001 \)), but not in the Caucasian population (\( P = 0.659 \)). This result indicated that survivin expression may only be involved in the progression of CIN lesions in the Asian population. Interestingly, when cervical cancer samples were compared to those of normal cervical tissues, subgroup analysis of ethnicity revealed that survivin expression was significantly correlated with...
cervical cancer risk in both the Asian and the Caucasian populations. However, the findings of the subgroup analysis should be carefully considered as only a small subject sample size was analyzed in the comparison between cancer and chronic cervicitis.

Our comparative analysis of cervical cancer vs. CIN lesions and chronic cervicitis indicated the presence of significant heterogeneity ($I^2 = 75.4\%$, $p < 0.001$; $I^2 = 56.1\%$, $p = 0.058$; respectively). Thus, we conducted meta-regression analyses to find the sources of heterogeneity. The results showed that ethnicity or expression location did not cause heterogeneity. Next, by deleting one study, we performed sensitivity analyses to estimate the influence and stability of the combined OR. In cervical cancer vs. CIN lesions, we deleted 4 studies and the overall OR (OR = 5.94, 95% CI = 4.30–8.19) remained significant, with no evidence of heterogeneity ($p = 0.253$ and $I^2 = 19.4\%$). In cervical cancer vs. chronic cervicitis, one study was removed and the pooled OR was significant (OR = 13.79, 95% CI: 6.26–30.34), with absence of heterogeneity ($p = 0.485$ and $I^2 = 0.0\%$). Sensitivity analyses results indicated the stability and credibility of our analyses.

Further, we determined whether survivin expression was correlated with the clinicopathological features of cervical cancer. Our findings demonstrated that survivin expression was correlated with tumor grade, where it was significantly higher in high-grade than in low-grade cervical cancer. In addition, survivin expression was correlated with the clinical stage, and it was significantly higher in advanced-stage patients than in early-stage patients. The expression of survivin was also associated with the lymph node status and was significantly higher in the cases with lymph node metastasis than in those without lymph node metastasis. The result suggests that the expression of survivin may play an important role in the progression and metastasis of cervical cancer. Therefore, we can conclude that survivin expression may serve as a potential drug target for cervical cancer therapy. In addition, we also found that survivin expression was correlated with the histological subtype and was slightly higher in SCC than in AC (OR = 1.99, $P = 0.045$), which indicated that survivin expression may exert more
substantial functions in the pathogenesis of SCC than in that of AC.

The current study has several limitations. First, although the abovementioned electronic databases were searched to minimize the possible publication bias, a slight publication bias was observed in the comparison of cancer vs. normal cervical tissues and chronic cervicitis concerning the cancer histological subtype ($P = 0.033$, $P = 0.034$, and $P = 0.023$, respectively). There could be several reasons for the bias identified. For example, the publications with positive results are generally more easily published than the ones with negative results. Additionally, papers in languages other than English and other types of publications, such as conference abstracts, could have been omitted due to insufficient information. Second, our study involved only Asians and Caucasians, and the participation of other ethnic groups was limited. Third, in the comparison between SCC and AC, only 55 patients with AC were included in this study. Additional studies with a larger sample size should be conducted in the future to confirm our findings.

In conclusion, our results revealed a higher expression level of survivin in cervical cancer than in CIN lesions, normal cervical tissues, and chronic cervicitis. The expression of survivin was more elevated in high-grade patients than in low-grade patients, in advanced-stage patients than in early-stage patients, in lymph node metastasis than in lymph node without metastasis, and in SCC than in AC. In addition, in the comparison between cervical cancer and CIN lesions, the subgroup analysis in terms of ethnicity indicated that survivin expression was significantly associated

![Figure 6. Forest plot of the association between survivin expression and lymph node status, 7 studies involving 200 lymph node positive patients with cervical cancer and 201 lymph node negative patients with cervical cancer: OR = 8.20, 95% CI = 4.09–16.45, $P < 0.001$.](image)

### Table 3. Meta-regression analyses in cancer vs. CIN lesions and chronic cervicitis.

| Cancer vs. CIN lesions | Coefficient (95% CI) | t | P-value |
|------------------------|----------------------|---|---------|
| Ethnicity              | −1.003 (−2.993, 0.987) | −1.09 | 0.296  |
| Expression location    | 0.107 (−1.602, 1.716)  | 0.14 | 0.888  |
| Cancer vs. chronic cervicitis | −0.359 (−6.507, 5.789) | −0.19 | 0.864  |

CIN: cervical intraepithelial neoplasia; 95% CI: 95% confidence intervals.
with cervical cancer in the Asian population, but not in the Caucasian population. Conducting further large-scale research is essential to validate our results in the future.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

**Funding**

This study was supported by funding (No. CS201515) from the Sci-Tech Development Project of Changshu City, Suzhou, Jiangsu, China.

**References**

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65(2):87-108; PMID:25651787; https://doi.org/10.3322/caac.21262

[2] Yeasmin S, Nakayama K, Rahman MT, Rahman M, Ishikawa M, Katagiri A, Iida K, Nakayama N, Otsuki Y, Kobayashi H, Nakayama S, Miyazaki K. Biological and clinical significance of NAC1 expression in cervical carcinomas: a comparative study between squamous cell carcinomas and adenocarcinomas/adenosquamous carcinomas. Hum Pathol 2012; 43(4):506-19; PMID:21889186; https://doi.org/10.1016/j.humpath.2011.05.021

[3] Winer I, Alvarado-Cabreiro I, Hassan O, Ahmed QF, Alish B, Bandypadhyay S, Thomas S, Albayrak S, Talukdar S, Al-Wahab Z, et al. The prognostic significance of histologic type in early stage cervical cancer - A multi-institutional study. Gynecol Oncol 2015; 137(3):474-8; PMID:25677061; https://doi.org/10.1016/j.ygyno.2015.02.005

[4] Ozden S, Tiber PM, Ozgen Z, Ozyurt H, Serakinci N, Orun O. Expression of TRF2 and its prognostic relevance in advanced stage cervical cancer patients. Biomed Res Int 2014; 47:61; PMID:25654471; https://doi.org/10.1186/0717-6287-47-61

[5] Robati M, Holtz D, Dunton CJ. A review of topotecan in combination chemotherapy for advanced cervical cancer. Therapeutics Clin Risk Management 2008; 4(1):213-8; PMID:18728710

[6] Pavlidou A, Dalamaga M, Kroupis C, Konstantoudakis G, Belimezi M, Athanasas G, Dimas K. Survivin isoforms and clinicopathological characteristics in colorectal adenocarcinomas using real-time qPCR. World J Gastroenterol 2011; 17(12):1614-21; PMID:21472129; https://doi.org/10.3748/wjg.v17.i12.1614
[7] Barinaga M. Death by dozens of cuts. Science 1998; 280(5360):32-4; PMID:9556450; https://doi.org/10.1126/science.280.5360.32

[8] Thompson CB. Apoptosis in the pathogenesis and treatment of disease. Science 1995; 267(5203):1456-62; PMID:7878464; https://doi.org/10.1126/science.7878464

[9] Rauch A, Hennig D, Schaefer C, Wirth M, Marx C, Heinzl T, Schneider G, Kramer OH. Survivin and YM155: how faithful is the liaison? Biochim Biophys Acta 2014; 1845(2):202-20; PMID:24440709

[10] Ambrosini G, Adida C, Sirugo G, Altieri DC. Induction of apoptosis and inhibition of cell proliferation by survivin gene targeting. J Biol Chem 1998; 273(18):11177-82; PMID:9556606; https://doi.org/10.1074/jbc.273.18.11177

[11] Sah NK, Khan Z, Khan GJ, Bisen PS. Structural, functional and therapeutic biology of survivin. Cancer Lett 2006; 244(2):164-71; PMID:16621243; https://doi.org/10.1016/j.canlet.2006.03.007

[12] Mita AC, Mita MM, Nawrocki ST, Giles FJ. Survivin: key regulator of mitosis and apoptosis and novel target for cancer therapeutics. Clin Cancer Res 2008; 14(16):5000-5; PMID:18698017; https://doi.org/10.1158/1078-0432.CCR-08-0746

[13] Altieri DC. Validating survivin as a cancer therapeutic target. Nat Rev Cancer 2003; 3(1):46-54; PMID:12509766; https://doi.org/10.1038/nrc968

[14] Stobiecka M, Dworakowska B, Jakiela S, Lukasiak A, Chalupa A, Zembrzycki K. Sensing of survivin mRNA in malignant astrocytes using graphene oxide nanocarrier-supported oligonucleotide molecular beacons. Sensors Actuators B: Chem 2016; 235:136-45; https://doi.org/10.7314/APJCP.2014.15.13.5271

[15] Stobiecka M, Chalupa A, Dworakowska B. Piezometric biosensors for anti-apoptotic protein survivin based on buried positive-potential barrier and immobilized monoclonal antibodies. Biosensors Bioelectronics 2016; 84:37-43; PMID:26507667; https://doi.org/10.1016/j.bios.2015.10.041

[16] Frost M, Jarboe EA, Orlicky D, Gianani R, Thompson LC, Enomoto T, Shroyer KR. Immunohistochemical localization of survivin in benign cervical mucosa, cervical dysplasia, and invasive squamous cell carcinoma. Am J Clin Pathol 2002; 117(5):738-44; PMID:12090422; https://doi.org/10.1016/S0002-9378(02)00204-1

[17] Kim HS, Shiraki K, Park SH. Expression of survivin in CIN and invasive squamous cell carcinoma of uterine cervix. Anticancer Res 2002; 22(2A):805-8; PMID:12014654

[18] Zintzaras E, Ioannidis JP. HEGESMA: genome search meta-analysis and heterogeneity testing. Bioinformatics 2005; 21(18):3672-3; PMID:15955784; https://doi.org/10.1093/bioinformatics/bti536

[19] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327(7414):557-60; PMID:12958120; https://doi.org/10.1136/bmj.327.7414.557

[20] DerSimonian R. Meta-analysis in the design and monitoring of clinical trials. Stat Med 1996; 15(12):1237-48; discussion 1249-1252; PMID:8817798; https://doi.org/10.1002/(SICI)1097-0258(19960630)15:12<1237::AID-SIM301>3.0.CO;2-N

[21] Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127(9):820-6; PMID:9382404; https://doi.org/10.7326/0003-4819-127-9-199711010-00008

[22] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315(7109):629-34; PMID:9310563; https://doi.org/10.1136/bmj.315.7109.629

[23] Zhou XL, Wang M. Expression levels of survivin, Bcl-2, and KAI1 proteins in cervical cancer and their correlation with metastasis. Genet Mol Res 2015; 14(4):17059-67; PMID:26681053; https://doi.org/10.4238/2015.December.16.6

[24] Liu HQ, Wang YH, Wang LL, Hao M. P16INK4A and survivin: Diagnostic and prognostic markers in cervical intraepithelial neoplasia and cervical squamous cell carcinoma. Exp Mol Pathol 2015; 99(1):44-9; PMID:25910412; https://doi.org/10.1016/j.yexmp.2015.04.004

[25] Zhou WQ, Sheng QY, Sheng YH, Hou WJ, Xu GX, Wu YM, Lu H. Expressions of survivin, P16(INK4a), COX-2, and Ki-67 in cervical cancer progression reveal the potential clinical application. Eur J Gynaecological Oncol 2015; 36(1):62-8

[26] Demir F, Kimiloglu E, Igdem AA, Ayanoglu YT, Erdogan N. High risk HPV in situ hybridization, p16 INK 4A, and survivin expressions in cervical carcinomas and intraepithelial neoplasms: evaluation of prognostic factors. Eur J Gynaecological Oncol 2014; 35(6):708-17; PMID:25556279

[27] Cao XQ, Lu HS, Zhang L, Chen LL, Gan MF. MEKK3 and survivin expression in cervical cancer: association with clinicopathological factors and prognosis. Asian Pac J Cancer Prev 2014; 15(13):5271-6; PMID:25040987; https://doi.org/10.7314/APJCP.2014.15.13.5271

[28] Kim SA, Hong R. Significance of intracellular localization of survivin in cervical squamous cell lesions: Correlation with disease progression. Oncol Lett 2014; 7(5):1589-93; PMID:24765182

[29] Lu D, Qian J, Yin X, Xiao Q, Wang C, Zeng Y. Expression of PTEN and survivin in cervical cancer: promising biological markers for early diagnosis and prognostic evaluation. Br J Biomedical Sci 2012; 69(4):143-6; PMID:23310986

[30] Wu SF, Zhang JW, Qian WY, Yang YB, Liu Y, Dong Y, Zhang ZB, Zhu YP, Feng YJ. Altered expression of survivin, Fas and FasL contributed to cervical cancer development and metastasis. Eur Rev Medical Pharmacological Sci 2012; 16(15):2044-50; PMID:23280017

[31] Bai H, Ge S, Lu J, Qian G, Xu R. Hypoxia inducible factor-1alpha-mediated activation of survivin in cervical cancer cells. J Obstetrics Gynaecol Res 2013; 39(2):555-63; PMID:22925504; https://doi.org/10.1111/j.1447-0756.2012.01995.x

[32] Barbosa LC, da Silva ID, Correa JC and Ribalta JC. Survivin and telomerase expression in the uterine cervix of
women with human papillomavirus-induced lesions. Int J Gynecological Cancer 2011; 21(1):15-21; PMID:21330827

[33] Tan GC, Norlatiffah S, Sharifah NA, Razmin G, Shiran MS, Hatta AZ, Paul-Ng HO. Immunohistochemical study of p16 INK4A and survivin expressions in cervical squamous neoplasm. Indian J Pathol Microbiol 2010; 53 (1):1-6; PMID:20090212; https://doi.org/10.4103/0377-4929.59173

[34] Yaqin M, Runhua L, Fuxi Z. Analyses of Bcl-2, Survivin, and CD44v6 expressions and human papillomavirus infection in cervical carcinomas. Scandinavian J Infect Dis 2007; 39(5):441-8; PMID:17464868; https://doi.org/10.1080/00365540601105772

[35] Lu S, Zhang B, Wang Z. Expression of survivin, cyclinD1, p21(WAF1), caspase-3 in cervical cancer and its relation with prognosis. J Huazhong Univ Sci Technol Med Sci 2005; 25(1):78-81; https://doi.org/10.1007/BF02831393

[36] Branca M, Giorgi C, Santini D, Di Bonito L, Giotti M, Costa S, Benedetto A, Casolati EA, Favalli C, Paba P, et al. Survivin as a marker of cervical intraepithelial neoplasia and a predictor of virus clearance and prognosis in cervical cancer. Am J Clin Pathol 2005; 124(1):113-21; PMID:15923164; https://doi.org/10.1309/L8BWF431WU9AC8FJ

[37] Lee JP, Chang KH, Han JH, Ryu HS. Survivin, a novel anti-apoptosis inhibitor, expression in uterine cervical cancer and relationship with prognostic factors. Int J Gynecological Cancer 2005; 15(1):113-9; PMID:15670305; https://doi.org/10.1111/j.1048-891X.2005.15011.x

[38] Singh A, Sharma H, Salhan S, Gupta SD, Bhatla N, Jain SK, Singh N. Evaluation of expression of apoptosis-related proteins and their correlation with HPV, telomerase activity, and apoptotic index in cervical cancer. Pathobiol 2004; 71(6):314-22; PMID:15627842; https://doi.org/10.1159/000081727

[39] Martin CM, O’Leary JJ. Histology of cervical intraepithelial neoplasia and the role of biomarkers. Best Practice Res Clin Obstetrics Gynaecol 2011; 25(5):605-15; PMID:21636328; https://doi.org/10.1016/j.bpobgyn.2011.04.005

[40] Wright TC, Jr, Cox JT, Massad LS, Carlson J, Twiggs LB, Wilkinson EJ, Workshop AS-sc. 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. J Lower Genital Tract Dis 2003; 7 (3):154-67; PMID:17051063; https://doi.org/10.1097/00128360-200307000-00002

[41] Johnson ME, Howarth EW. Survivin: a bifunctional inhibitor of apoptosis protein. Veterinary Pathol 2004; 41 (6):599-607; PMID:15557069; https://doi.org/10.1354/vp.41-6-599