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Pelvic inflammatory disease increases the risk of a second primary malignancy in patients with cervical cancer treated by surgery alone

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Abstract

As the number of long-term cervical cancer survivors continues to increase because of improvements in treatment, concerns about second primary malignancy have grown. The high-risk area of second primary cancers in cervical cancer survivors is the pelvis. Pelvic inflammatory disease (PID) could be a useful marker for gynecological cancers. Thus, we designed a large-scale, nationwide, controlled cohort study to investigate whether PID or other risk factors increased the risk of second primary cancers in patients with cervical cancer treated by surgery alone.

Between 2000 and 2010, a total of 24,444 cervical cancer patients were identified using the Registry Data for Catastrophic Illness and the National Health Insurance Research Database (NHIRD) of Taiwan. Patients who received definite surgery were selected. To exclude the effect on second primary malignancy by treatment modalities, all cervical patients who ever having received adjuvant or definite radiotherapy or chemotherapy for primary cervical cancer were excluded. Finally, 3860 cervical cancer patients treated by surgery alone without adjuvant treatments were analyzed.

Cox proportional hazards model was used for multivariate analysis and the Kaplan–Meier method was used to assess the cumulative risks. Regarding the incidence of second primary cancers, the standardized incidence ratio (SIR) was used.

The median follow-up time was 56.6 months. The 6-year cumulative risk of second primary cancers is 0.16% and 0.12% for PID and without PID, respectively. After adjustment for confounders, age of less than 50 years, the presence of diabetes mellitus, and PID were significantly positivity associated with the risk of second primary cancers. The hazard ratios (HRs) of age less than 50 years, diabetes mellitus, and PID were 1.38 (95% CI = 1.11–2.04), 1.40 (95% CI = 1.06–1.85), and 1.35 (95% CI = 1.00–1.81), respectively. A higher incidence of second primary cancers was observed in the genitals, bladder, and colon.

In conclusion, the incidence of second primary cancers was higher in the genitals, bladder, and colon in patients with cervical cancer treated with surgery alone. The patients with PID had a higher risk of second primary cancers.

Abbreviations: EC = enrollee category, HPV = human papillomavirus, HR = hazard ratio, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NTD = New Taiwan Dollar, PID = pelvic inflammatory disease, SIR = standardized incidence ratio, USD = United States Dollar.

Keywords: cervical cancer, pelvic inflammatory disease, second primary malignancy

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1. Introduction

Cervical cancer is the second most frequent cancer among women worldwide, and it remains an important and prevalent malignant disease in Taiwan.[1] Although cervical cancer of females has declined in Taiwan since beginning in 1995 because National Health Insurance (NHI) has provided free mass screening of cervical neoplasia since 1995. The national Pap smear screening program significantly reduced cervical cancer risk explaining the dramatic decline in invasive cancer incidence after 1996.[2] Cervical cancer was still the 7th prevalent cancer in women in Taiwan in 2013.[3] In 2006, there was an annual incidence rate of 16.2 per 100,000 people for invasive cervical cancer and a mortality rate of 7.8 per 100,000 people in Taiwan.[4] A study ever showed that the average lifetime costs (10 years) for cervical cancer were NT$511,563 in Taiwan (in 2012 NTD, 1USD≠NTD 33).[5]

The 3 primary treatment modalities for this disease are surgery, radiotherapy, and chemotherapy. As treatment improves with the introduction of new agents and modern techniques, the number of long-term cervical cancer survivors continues to increase, in addition to concerns about second primary malignancies. Radiotherapy has a critical role in the primary management of patients with cervical cancer, and it has been reported that radiotherapy increases the risk of second cancers at sites in close proximity to the cervix.[6] In addition to radiotherapy, chemotherapy, human papillomavirus (HPV) infection, and cigarette smoking elevate the risk for second primary cancers among cervical cancer survivors.[7] In an another nationwide population-based study in Taiwan, cervical cancer treatments, including both radiotherapy (HR = 1.27, 95% CI = 1.14–1.43) and chemotherapy (HR = 1.41, 95% CI = 1.25–1.59), were shown to increase secondary primary malignancy risk, but not surgery (HR = 0.94, 95% CI = 0.84–1.04).[8] For surgery, secondary primary cancer is not being considered as a substantial long-term clinical complication of cancer surgery, except in some breast, colon, and stomach cancer survivors, such as angiosarcoma in a lymphedema arm postaxillary lymph node dissection in breast cancers patients.[9] Interestingly, the high-risk area for second primary cancers in cervical cancer survivors is the pelvis, even among patients who did not receive radiotherapy.[6] Recently, pelvic inflammatory disease (PID) was identified as a useful marker for gynecological cancers.[10]

Thus, we designed a large-scale, nationwide, controlled cohort study to investigate whether PID and other risk factors increased the risk of second primary cancers in patients with cervical cancer treated with surgery alone without chemotherapy or radiotherapy.

2. Materials and methods

2.1. Ethics statement

This study was approved by the Institutional Review Board of Buddhist Dalin Tzu Chi General Hospital, and the approval number is B10001017. The procedures were performed in accordance with the ethical standards of the committee on human experimentation of our institution and the Declaration of Helsinki. The institutional review board waived the need for written informed consent from the participants because the analyzed data consisted of anonymous secondary data released to the public for research.

2.2. Patients and study design

The study analyzed 2000 to 2010 data from the National Health Insurance Research Database (NHIRD), provided by the National Research Institutes in Taiwan. The NHIRD contains the medical benefit claims for 97% of the population from a registry of board-certified physicians and contracted medical facilities. The database contains comprehensive information on insured subjects, including the dates of clinical visits, diagnostic codes, details about prescriptions, and expenditure amounts.

Data on each patient were collected starting from the first hospitalization or outpatient visit in 2000. Patients were initially identified as having cervical cancer according to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code 180, from Registry Data for Catastrophic Illness. Catastrophic illness certificate, a peer-confirmed data subset, which could further ensure the accuracy of a cancer diagnosis was used for validation of cancer diagnosis.[11]

We identified 24,444 patients who were newly diagnosed with cervical cancer confirmed by catastrophic illness certificates and between 2000 and 2010. Patients who received definite surgery were selected. To exclude the effect on second primary malignancy by treatment modalities, all cervical patients who ever having received adjuvant or definite radiotherapy or chemotherapy for primary cervical cancer were excluded (Fig. 1). Patients who underwent surgery before diagnosis, those who developed distant metastasis before surgery, were also excluded.

Finally, 3860 cervical cancer patients treated by surgery alone without adjuvant treatments were analyzed. Figure 1 shows the flow chart of patient selection. This cervical cancer cohort treated by surgery alone was divided into PID and non-PID groups.

The primary dependent variable was any secondary cancer (ICD-9-CM codes 140–165, 170–176, 179, 181–193, and 195–199). The adjusted independent variables included age, comorbidities, geographic region, urbanization level, and socioeconomic status. Comorbidities included hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), coronary heart disease (ICD-9-CM codes 410–414), hyperlipidemia (ICD-9-CM codes 2720–2724), PID (ICD-9-

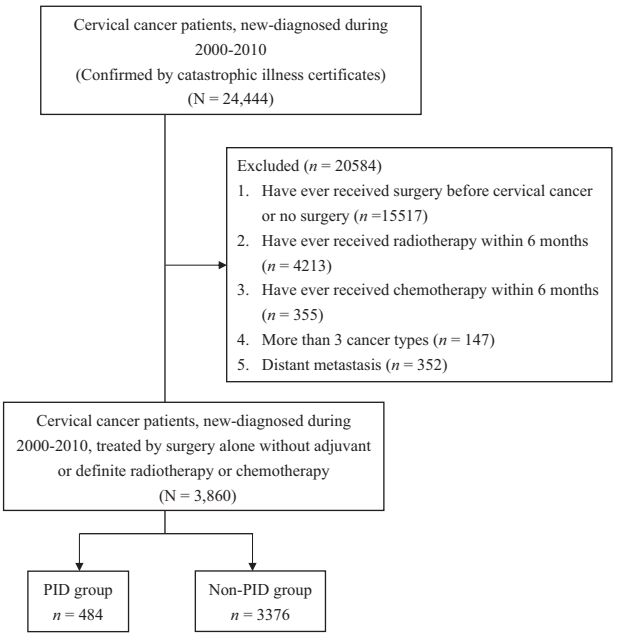

Figure 1. A flowchart presenting the selection and group allocation of the cervical cancer patients cohort treated by surgery alone without adjuvant or definite radiotherapy or chemotherapy divided into pelvic inflammatory disease (PID) and non-PID groups.

CM codes 614–616), and chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, and 496). For the purposes of the study, the country was divided into 4 geographic regions (Northern, Central, Southern, Eastern) and 3 urbanization levels (urban, suburban, rural). This study also used enrollee category (EC) as a proxy measure for socioeconomic status. All patients were categorized as EC1 (the highest socioeconomic status), EC2, EC3, EC4 (the lowest socioeconomic status), or other. The association of these variables with any second primary cancer was assessed.

Regarding the incidence of second primary cancers, the standardized incidence ratio (SIR) was used. In brief, we used the patients' ages at diagnosis for stratification and counted the numbers of second primary cancers (Y1) and person-years (X) in different age groups. We then calculated standardized rate numbers of cases (Y2) for comparison with the 2000 global standard population (A). The predicted risks for second primary cancer were estimated using the equation $Y2 = Y1 \times A/X$. According to this formula, we could obtain standardized rate numbers of cases for different cancers and years. Finally, we summed the number of cases (Yn). The health promotion administration announced the standardized rate per 100,000 people (Y0), and we could use these data as our reference. We could evaluate the SIR using the equation $SIR = Yn/Y0 \times 10^5$.

2.3. Statistical analysis

The statistical software packages SAS (version 9.2; SAS Institute, Inc., Cary, NC) and SPSS (version 17; SPSS, Inc., Chicago, IL) were used for data analysis. Pearson Chi-squared test was used to explore the differences between categorical variables in the different groups. The PID cumulative risk and survival rates were estimated using the Kaplan–Meier method and compared using the log-rank test. A Cox proportional hazard regression model was used to calculate the adjusted risk after adjusting for confounders. $P < 0.05$ was defined as statistically significant. The potential risk factors included age, comorbidities, geographic region, urbanization level, and socioeconomic status.

3. Results

The 5-year overall survival rate for all cervical cancer patients treated by surgery alone without adjuvant or definite radiotherapy or chemotherapy was 94.7%. The median follow-up time was 56.6 months. The characteristics and comorbidities of the patients included in the study are shown in Table 1. The SIR of second primary cancers is shown in Table 2. Higher frequencies of second primary cancers were observed in the genitals, bladder, and colon. The SIRs for these sites were 5.52 (95% CI = 3.02–6.12), 1.58 (95% CI = 1.12–2.34), and 1.47 (95% CI =

Table 1

Characteristics of cervical cancer patients treated by surgery alone without adjuvant or definite radiotherapy or chemotherapy.

	PID (+), N = 484		PID (−), n = 3376		
	n	%	n	%	*P*
Age, y					<0.001
0–44	262	54.1	1109	32.8	
45–54	138	28.5	1072	31.8	
55–64	64	13.2	588	17.4	
65–74	15	3.1	459	13.6	
75+	5	1	148	4.4	
Diabetes mellitus					0.73
Yes	69	14.3	501	14.8	
No	415	85.7	2875	85.2	
Hypertension					<0.001
Yes	90	18.6	970	28.7	
No	394	81.4	2406	713	
Coronary heart disease					0.95
Yes	71	14.7	492	14.6	
No	413	85.3	2884	85.4	
Hyperlipidemia					0.84
Yes	96	19.8	657	19.5	
No	388	80.2	2719	80.5	
Chronic obstructive pulmonary disease					0.43
Yes	70	14.5	445	13.2	
No	414	85.5	2931	86.8	
Urbanization level					0.89
Urban	140	28.9	994	29.4	
Suburban	229	47.3	1559	46.2	
Rural	115	23.8	823	24.4	
Geographic region					0.18
Northern	228	47.1	1593	47.2	
Central	132	27.3	835	24.7	
Southern	110	22.7	882	26.1	
Eastern	14	2.9	66	2.0	
EC					0.15
EC 1–2	178	36.8	1108	32.8	
EC 3–4	237	49.0	1826	54.1	
Other	69	14	442	13	

EC = enrollee category, PID = pelvic inflammatory disease.

Table 2

Standardized incidence ratio (SIR) of various second primary cancers.

Site	SIR	95% CI
Female genital sites*	5.52	3.02–6.12
Bladder	1.58	1.12–2.34
Colon	1.47	1.16–2.18
Breast	0.85	0.67–0.93
Lung	0.61	0.32–1.04
Esophagus	0.57	0.19–1.58
Skin	0.27	0.16–0.42
Liver	0.18	0.07–0.69

95% CI = 95% confidence interval.
* Female genital sites included ovary, uterus, major and minor labia, vagina, and fallopian tube.

1.16–2.18), respectively. Patients with PID had higher frequencies of second primary cancers (Fig. 2). The 6-year cumulative risk of second primary cancers is 0.16% and 0.12% for PID and without PID, respectively.

After adjustment for age, comorbidities, urbanization level, geographic region, and EC, the hazard ratios (HRs) for age less than 50 years, the presence of diabetes mellitus, and PID were statistical significant (Table 3). The HRs of age less than 50 years, diabetes mellitus, and PID were 1.38 (95% CI = 1.11–2.04), 1.40 (95% CI = 1.06–1.85), and 1.35 (95% CI = 1.00–1.81), respectively. Hypertension, coronary heart disease, hyperlipidemia, chronic obstructive pulmonary disease, urbanization level, geographic region, and EC were not statistical significant.

4. Discussion

Based on our population-based study using NHIRD data, the risks for second primary cancers of the genitals, bladder, and colon in women with surgically removed colon cancer were significantly elevated. Several series reported similar findings. A study using data from the Swedish Family-Cancer Database identified elevated SIRs for cancers of the aerodigestive tract, anus, pancreas, lung, genitals, and urinary bladder in women

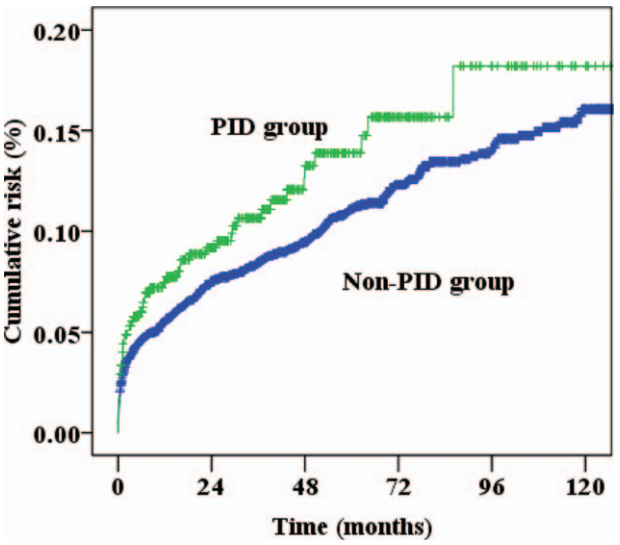

Figure 2. The risk of second primary cancers according to the presence or absence of pelvic inflammatory disease (PID).

Table 3

Crude and adjusted HRs for second primary cancers.

Variable	Adjusted HR	95% CI	*P*
Age < 50 y	1.38	(1.11–2.04)	0.04
Hypertension	0.92	(0.70–1.20)	0.56
Diabetes mellitus	1.40	(1.06–1.85)	0.01
Coronary heart disease	1.19	(0.89–1.59)	0.23
Hyperlipidemia	1.03	(0.78–1.36)	0.81
Pelvic inflammatory disease	1.35	(1.00–1.81)	0.04
Chronic obstructive pulmonary disease	1.02	(0.76–1.37)	0.88
Urbanization level			
Urban (ref.)	1		
Suburban	1.04	(0.81–1.33)	0.72
Rural	1.04	(0.76–1.41)	0.80
Geographic region			
Northern (ref.)	1		
Central	0.91	(0.69–1.18)	0.48
Southern	0.83	(0.64–1.08)	0.61
Eastern	0.82	(0.38–1.76)	0.18
EC			
EC 1–2 (ref.)	1		
EC 3–4	0.82	(0.66–1.03)	0.90
Other	0.96	(0.68–1.37)	0.84

CI = confidence interval, EC = enrollee category, HR = hazard ratio.

with in situ or invasive cervical cancer.[12] Kleinerman et al[13] also revealed that most second cancers arose in the rectum, vagina, vulva, ovaries, and bladder. Taken together, the area of greatest risk for second primary cancers in cervical cancer survivors is the pelvis.

Consistent with the presence of several established cancer risk factors among cervical cancer survivors, we identified age, diabetes mellitus, and PID as significant variables. In epidemiological findings, several studies reported low parity, nulliparity, and infertility as important risk factors for gynecological cancers and frequent complications of PID.[14–16] However, the conclusions of reported studies are inconsistent.[17] Recently, Lin et al[10] conducted a large-scale, nationwide, controlled cohort study and demonstrated that PID raised the risk of developing ovarian cancer. Specifically, multiple episodes of PID increased the risk of cancer in their study. Our study also found that patients with PID had higher rates of second primary cancers. After adjustment for confounding factors, PID remained a significant predictor. Chronic inflammation or infection could contribute to the development or activation of malignant disease.[18,19] PID might constitute a marker for gynecological cancers that could enable early treatment and improved prognosis.

In this study, women aged 50 years or younger who had PID had a higher risk of developing secondary primary malignancies than older women. Risch and Howe[16] uncovered that the risk of second primary cancer was increased in women with PID who were 20 years or younger. Manavi[20] reported that women between 16 and 19 years of age had the highest prevalence of chlamydial infection, and a proportion of these women eventually developed PID. Lin et al[10] further demonstrated that the risk of ovarian cancer increased with increasing frequency of PID episodes. Although differences in outcomes between ethnic groups were noted, younger women with PID might be at higher risk of recurrent episodes of PID and therefore at greater risk of secondary primary malignancy.

Epidemiological data indicate that diabetes increases the risk of cancer.[21] The frequencies of type 2 diabetes mellitus and

malignant tumors are increasing continuously, and these diseases cause serious health problems.[22] Population-based epidemiologic studies revealed that the coexistence of type 2 diabetes and malignant tumors is more frequent than expected according to the age-corrected incidence. In experiments studies, metabolic changes associated with hyperinsulinemia played an important role in the relationship between cancer and type 2 diabetes mellitus.[23] We also found that diabetes mellitus was an important factor influencing the risk of secondary primary malignancy. Importantly, women with diabetes were previously found to have an increased risk of PID.[24] Cancer is a complicated multistep process. Secondary primary malignancy presents a more complex situation. Recent studies illustrated that different treatment modalities, including various combinations of antidiabetic drugs, can modify cancer risk.[21,25] According to present knowledge, developing and utilizing optimal treatment modalities are suggested.

Our study had several limitations. First, the database does not contain information regarding the classification and severity of PID. However, the NHI covered approximately 97% of the island's population, and we could verify PID episodes. The trend identified in the study should not have been affected by the missing information. Second, almost all patients diagnosed as PID would receive treatments in Taiwan, because most residents in Taiwan are covered by NHI program and the treatment fee is free. Therefore, it could not differentiate whether no treatment of PID would further increase the risk of secondary malignancy in this study. Third, HPV is a cause of cervical cancer, vaginal cancer, vulva cancer and should be incorporated into this secondary malignancy study. However, there is no data about HPV vaccination in our NHIRD database because HPV vaccination is still self-paid, not covered by NHI and is therefore not included in NHIRD. However, HPV prevalence is relatively low in Asia compared to that in non-Asian areas (11–19% vs 57–75%).[26,27] The importance of HPV infection was likely reduced in our cohort. Fourth, tobacco use might be a risk factor for secondary primary cancers.[28] The database does not contain this information. However, tobacco use is correlated with chronic obstructive pulmonary disease. We used chronic obstructive pulmonary disease instead of tobacco use for adjustment. Taken together and given the robustness of both the evidence and statistical analyses used in this study, these limitations are unlikely to have compromised our results.

Cervical cancer treatment strategy could not be affected by our study findings because patients in our study all received surgery and all not received radiotherapy or chemotherapy. Cancer treatment response is still the first priority to be considered because of the high mortality and low incidence of second malignancy. However, PID should be treated or prevented in cervical cancer patients because our study showed PID is a risk factor of second malignancy even after adjustment of several possible contributing factors.

For survey of the possible second malignancy, healthcare provider or clinical physicians should pay more attention to cervical cancer patients who has risk factors, like young age, history of PID, diabetes mellitus, and especially to these sites, including female genital organs, bladder, and colon.

In conclusion, higher frequencies of second primary cancers were observed in the genitals, bladder, and colon in women with cervical cancer treated via surgery alone. Patients with PID had higher incidences of second primary cancers.

References

[1] Tsai SJ, Huang YS, Tung CH, et al. Increased risk of ischemic stroke in cervical cancer patients: a nationwide population-based study. Radiat Oncol 2013;8:41.

[2] Chiang CJ, Chen YC, Chen CJ, et al. Cancer trends in Taiwan. Jpn J Clin Oncol 2010;40:897–904.

[3] MOHW. The Ministry of Health and Welfare Announces the 2013 Cancer Incidence Data; Colorectal Cancer Continues to Be on Top. 2016; Available at: http://www.mohw.gov.tw/EN/Ministry/DM2_P.aspx?f_list_no=378&fod_list_no=5760&doc_no=54431. Accessed 10/03, 2016.

[4] Taiwan Cancer Registry, Department of Health (Taiwan). Cancer Incidence and Mortality Rates in Taiwan. Available at: http://crs.cph.ntu.edu.tw/uploadimages/Leading_10.pdf. 2006. Accessed 10/03, 2016.

[5] Lang HC, Wu SL. Lifetime costs of the top five cancers in Taiwan. Eur J Health Econ 2012;13:347–53.

[6] Chaturvedi AK, Engels EA, Gilbert ES, et al. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. J Natl Cancer Inst 2007;99:1634–43.

[7] Hemminki K, Dong C, Vaittinen P. Second primary cancer after in situ and invasive cervical cancer. Epidemiology 2000;11:457–61.

[8] Teng CJ, Huon LK, Hu YW, et al. Secondary primary malignancy risk in patients with cervical cancer in Taiwan: a nationwide population-based study. Medicine (Baltimore) 2015;94:e1803.

[9] Schwab M. Second Primary Tumors. Encyclopedia of Cancer 3rd ed. Berlin, Heidelberg:Springer-Verlag; 2012. 2676.

[10] Lin HW, Tu YY, Lin SY, et al. Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. Lancet Oncol 2011;12:900–4.

[11] Chen HF, Chen P, Li CY. Risk of malignant neoplasms of liver and biliary tract in diabetic patients with different age and sex stratifications. Hepatology 2010;52:155–63.

[12] Levi F, Te VC, Randimbison L, et al. Second primary cancers after in situ and invasive cervical cancer. Epidemiology 2001;12:281–2.

[13] Kleinerman RA, Boice JDJr, Storm HH, et al. Second primary cancer after treatment for cervical cancer. An international cancer registries study. Cancer 1995;76:442–52.

[14] Purdie DM, Bain CJ, Siskind V, et al. Ovulation and risk of epithelial ovarian cancer. Int J Cancer 2003;104:228–32.

[15] Chiaffarino F, Pelucchi C, Negri E, et al. Breastfeeding and the risk of epithelial ovarian cancer in an Italian population. Gynecol Oncol 2005;98:304–8.

[16] Risch HA, Howe GR. Pelvic inflammatory disease and the risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prevent 1995;4:447–51.

[17] Parazzini F, La Vecchia C, Negri E, et al. Pelvic inflammatory disease and risk of ovarian cancer. Cancer Epidemiol Biomarkers Prevent 1996;5:667–9.

[18] von Hertzen LC, Joensuu H, Haahtela T. Microbial deprivation, inflammation and cancer. Cancer Metastasis Rev 2011;30:211–23.

[19] Vinchant M, Poncelet C, Ziol M, et al. Malignant transformation of abdominal wall endometriosis: case report and literature review. Tumori 2013;99:e49–54.

[20] Manavi K. A review on infection with Chlamydia trachomatis. Best Pract Res Clin Obstet Gynaecol 2006;20:941–51.

[21] Tokajuk A, Krzyzanowska-Grycel E, Tokajuk A, et al. Antidiabetic drugs and risk of cancer. Pharmacol Rep 2015;67:1240–50.

[22] Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–85.

[23] Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. Physiol Rev 2015;95:727–48.

[24] Diamond MP, Entman SS, Salyer SL, et al. Increased risk of endometritis and wound infection after cesarean section in insulin-dependent diabetic women. Am J Obstet Gynecol 1986;155:297–300.

[25] Pandey A, Forte V, Abdallah M, et al. Diabetes mellitus and the risk of cancer. Minerva Endocrinol 2011;36:187–209.

[26] Hammer A, Rositch A, Qeadan F, et al. Age-specific prevalence of HPV16/18 genotypes in cervical cancer: a systematic review and meta-analysis. Int J Cancer 2016;138:2795–803.

[27] Tay SK, Ngan HY, Chu TY, et al. Epidemiology of human papillomavirus infection and cervical cancer and future perspectives in Hong Kong, Singapore and Taiwan. Vaccine 2008;26(suppl 12):M60–70.

[28] Crotty Alexander LE, Shin S, Hwang JH. Inflammatory diseases of the lung induced by conventional cigarette smoke: a review. Chest 2015;148:1307–22.