Climacteric Symptoms in Postoperative Patients Among Endometrial Cancer, Cervical Cancer, and Ovarian Cancer: A Cross-Sectional Study

YUKO HORIBA (✉ mannta217@keio.jp)

Keio University: Keio Gijuku Daigaku <https://orcid.org/0000-0003-3260-6755>

Tetsuhiro Yoshino

Keio University: Keio Gijuku Daigaku

Megumi Yokota

Keio University: Keio Gijuku Daigaku

Takashi Iwata

Keio University: Keio Gijuku Daigaku

Kenji Watanabe

Keio University: Keio Gijuku Daigaku

Masaru Mimura

Keio University: Keio Gijuku Daigaku

Daisuke Aoki

Keio University: Keio Gijuku Daigaku

Research article

Keywords: gynecologic cancer survivors, climacteric, patient-reported outcome, health related quality of life, postoperative period, adnexectomy, hysterectomy

Posted Date: December 7th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-121103/v1>

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Abstract

Background: No studies have assessed climacteric symptoms after hysterectomy for endometrial, cervical, or ovarian cancer. Thus, this study aimed to compare climacteric symptoms among patients who underwent surgery for these three cancer types.

Methods: We included patients who were registered at a menopausal outpatient clinic between January 1999 and July 2016 after undergoing total hysterectomy, intrapelvic only or intrapelvic plus para-aortic lymph node dissection, and bilateral adnexectomy performed via laparotomy as cancer treatment. The numbers of patients with endometrial, ovarian, and cervical cancer were 328, 90, and 107, respectively. We collected the following data: age at surgery, time since surgery, body mass index, menopausal status at surgery, and postoperative adjuvant therapy. Climacteric symptoms were assessed using a patient-reported questionnaire covering 40 parameters. Each symptom was graded from 0 (no symptoms) to 3 (severe symptoms). The total for all 40 parameters was considered as the degree of symptom severity.

Results: Multivariate analysis revealed that time since surgery and cancer type had statistically significant effects on climacteric symptom severity. Overall, climacteric symptoms were more severe in patients with cervical cancer than in those with endometrial or ovarian cancer; symptom severity decreased with increasing time since surgery. However, in patients with cervical cancer, symptom severity did not decrease significantly over time, even after >5 years had elapsed since surgery.

Conclusions: The severity of climacteric symptoms decreased with time after surgery for patients with endometrial or ovarian cancer but not for those with cervical cancer. Patients with cervical cancer may require more prompt interventions, including symptomatic treatment, and longer follow-up than those with endometrial or ovarian cancer.

Background

Gynecological cancer has major societal and economic implications, partly because of cancer treatment-related infertility and the role of women in the workforce. The annual number of gynecological cancer cases worldwide is 382,069 for endometrial cancer; 295,414 for ovarian cancer; and 569,847 for cervical cancer, and these cancers were the 16th, 19th, and 9th most common types of cancer in 2018, respectively [1]. The 5-year survival rate of patients with gynecological cancer is relatively higher than that of patients with other cancer types [2, 3]; hence, there are many gynecologic cancer survivors.

Long-term gynecologic cancer survivors have significant mental or psychological symptoms [4, 5], but usage of only overall scales of quality of life (QOL), including socioeconomic and family domains in addition to the health-related domain, would be inappropriate to evaluate the survivors' status or satisfaction. For example, patients with cervical and short-survival (esophagus, liver, lung, pancreas, and stomach) cancers have lower physical and mental health-related QOL (HRQOL) than do adults with no cancer history [6]. However, no significant difference was found in the overall QOL between patients with gynecological cancer and adults with no cancer history [7, 8]. Moreover, ovarian cancer survivors report

good QOL scores but have impaired sexual function and climacteric symptoms [9]. Another study showed that more than half of gynecologic cancer survivors have sexual health concerns [10], especially those surviving from cervical cancer [11]. Therefore, further studies focusing on specific symptoms for gynecologic cancer survivors but not on the overall QOL score are needed. Moreover, these results are indicative of the need to evaluate differences among these gynecological cancer types, namely cervical, ovarian, and endometrial.

Depending on the cancer stage, bilateral adnexectomy is sometimes required to treat gynecological cancer. Treatment of gynecological cancer via uterine and/or ovarian resection is considered to have marked physical and mental effects that are specific to gynecological cancer, including loss of sense of femininity and complications affecting the pelvic organs and lymph nodes. Gynecological cancer tends to affect women in their 40 s and 50 s [12, 13], which is around 50 years of age when many women experience their menopause [14, 15]. In premenopausal patients, adnexectomy results in artificial menopause, and it is common for patients to present climacteric symptoms [16, 17]. Considering the long-life expectancy of such cancer survivors after bilateral adnexectomy, climacteric symptoms may play a role in QOL [18]. Understanding the risk factors associated with worse climacteric symptoms will help identify these individuals and aid in planning interventions for endometrial, ovarian, and cervical cancer. However, there have been no reports on climacteric symptoms after hysterectomy for these three cancer types.

The present study aimed to compare the climacteric symptoms among patients who underwent surgery for endometrial, cervical, or ovarian cancer in an outpatient clinic.

Methods

Study setting and patients

This study included patients who were treated at a menopausal outpatient clinic between January 1999 and July 2016. The inclusion criteria were as follows: (i) a histological diagnosis of endometrial, ovarian, or cervical cancer; (ii) postmenopausal state at each first consultation due to total hysterectomy, intrapelvic only or intrapelvic plus para-aortic lymph node dissection, and bilateral adnexectomy performed by laparotomy as cancer treatment; and, if applicable, (iii) completed adjuvant therapy, such as chemotherapy or radiotherapy, at the first consultation, even after recurrence.

Patients were excluded from the analysis if data were missing, i.e., if the body mass index was not recorded, and/or if one or more of the following was unknown: date of surgery; performance or non-performance and details of adjuvant therapy (chemotherapy and/or radiotherapy); and pre- or postmenopausal status at surgery.

Questionnaire

At initial examination, subjects were interviewed using a patient-reported questionnaire comprising 40 questions (Supplementary Table 1), prepared on the basis of Kupperman's menopausal index [19–21].

Each of the patients' symptoms was graded on a 4-point scale as follows: 0, no symptoms; 1, mild symptoms (that is, symptoms that did not affect activities of daily life); 2, moderate symptoms (that is, symptoms that affected activities of daily life to some degree); and 3, severe symptoms (that is, symptoms that markedly affected activities of daily life). The total score for all 40 parameters was considered as the degree of symptom severity.

Statistical analysis

Basic characteristics of the study patients were compared using Kruskal-Wallis test for sequential items in three or more groups and chi-squared test for nominal categories in two groups. We performed a linear regression analysis to compare the effects of independent variables on the degree of symptom severity. The independent variables included cancer type, age at surgery, time since surgery, body mass index, menopausal status at surgery, whether or not chemotherapy was performed, and whether or not radiotherapy was performed. There were two patients, one with cervical and one with ovarian cancer, who had received neoadjuvant chemoradiation therapy and chemotherapy, respectively; we did not differentiate these patients in this analysis. After univariate analysis, the data were adjusted using multivariate analysis. As sensitivity analysis, patients were divided into three groups according to their age at first consultation: (i) < 45 years, (ii) 45–55 years, and (iii) > 55 years; the time since surgery: (i) < 1 year, (ii) 1–5 years, and (iii) > 5 years; and their body mass index: (i) < 18.5 kg/m², (ii) 18.5–25 kg/m², and (iii) > 25 kg/m². All statistical analyses were conducted using R software, version 4.0.1 (The R Foundation for Statistical Computing; June 6, 2020). We used “glm” from the package “stats” and “DAAG” for regression analysis. We used a significant level of 5% for all tests.

Results

Baseline characteristics of the study patients

A total of 780 patients were examined between January 1999 and July 2016, of whom 525 met the inclusion criteria (Fig. 1). Of these 525 patients, 328 had endometrial cancer, 90 had ovarian cancer, and 107 had cervical cancer. The baseline characteristics of patients in each of the three groups are shown in Table 1. Compared with patients with cervical or ovarian cancer, those with endometrial cancer were significantly older at the initial examination, had significantly higher body mass index, were significantly older at surgery, and significantly more of them had passed natural menopause. Among patients with cervical cancer, 26% were premenopausal at surgery. Among patients with cervical cancer, 13% had received radiotherapy after laparotomic surgery. None of the patients with endometrial or ovarian cancer had received chemoradiotherapy as adjuvant therapy.

Table 1
Baseline characteristics of the study patients

Characteristics	Endometrioid cancer	Ovarian cancer	Cervical cancer	P value
N	328	90	107	
Age at first consultation, years	57 (26–84)	45.5 (30–75)	43 (23–78)	< 0.001
Age at surgery, years	50 (24–60)	44 (26–56)	40.5 (23–56)	< 0.001
Time since surgery, months	31 (1–333)	25 (1–212)	20 (1–366)	0.343
Time since surgery, N (%)				
< 1 year	84 (25.6)	20 (22.2)	34 (31.8)	0.291
1–5 years	132 (40.2)	46 (51.1)	44 (41.1)	
> 5 years	112 (34.1)	24 (26.7)	29 (27.1)	
Body mass index, kg/m ²	22.1 (12.6–38.1)	20.5 (15.5–28.9)	20.3 (13.0–30.0)	< 0.001
Body mass index, N (%)				
< 18.5 kg/m ²	35 (10.7)	17 (18.9)	20 (18.7)	< 0.001
18.5–25 kg/m ²	211 (64.3)	66 (73.3)	79 (73.8)	
> 25 kg/m ²	82 (25.0)	7 (7.8)	8 (7.5)	
Menopausal status at surgery, N (%)				
Premenopausal	3 (0.9)	2 (2.2)	28 (26.2)	< 0.001
Postmenopausal	325 (99.1)	88 (97.8)	79 (73.8)	
Additional treatment, N (%)				
Chemotherapy only	83 (25.3)	56 (62.2)	32 (29.9)	< 0.001
Radiation only	5 (1.52)	0 (0.0)	7 (6.5)	
Chemoradiation	0 (0.0)	0 (0.0)	7 (6.5)	
None	240 (73.2)	34 (37.8)	61 (57.0)	
Data represent the median (range) unless otherwise indicated.				

Univariate and multivariate analysis

Univariate analysis of baseline characteristics revealed that the degree of symptom severity was significantly associated with three independent variables: age at surgery, time since surgery, and cancer type (Table 2). In multivariate analysis, the effect of age at surgery became insignificant, and only time since surgery and cancer type were significantly associated with total symptom severity. The degree of symptom severity was equal to $29.8 - 0.49 (\text{time since surgery, year}) + 5.2 (\text{if ovarian cancer}) + 6.3 (\text{if cervical cancer})$. This equation means that symptom severity decreases with increasing time since surgery and increases if the cancer type is ovarian or cervical cancer (Fig. 2). This significance was consistent even if time since surgery was converted into a categorical variable with the treating time since surgery as a categorical variable.

Table 2
Univariate and multivariate analyses

Parameters	Univariate analysis			Multivariate analysis		
	Estimate	Standard error	P value	Estimate	Standard error	P value
Age at surgery, years	-0.30	0.10	< 0.01	-0.13	0.11	0.24
Time since surgery, years	-0.49	0.15	< 0.01	-0.49	0.15	< 0.01
Body mass index, kg/m ²	-0.076	0.18	0.66	0.13	0.18	0.45
Menopause at surgery, yes/no	-3.9	1.8	0.035	-1.3	2.0	0.53
Chemotherapy, yes/no	-0.23	1.6	0.88	-2.6	1.6	0.12
Radiation, yes/no	4.3	4.0	0.28	1.9	4.1	0.64
Cancer type						
Endometrial cancer	-6.3	1.5	< 0.01	-	-	-
Ovarian cancer	3.1	2.0	0.12	5.2	2.1	0.015
Cervical cancer	6.4	1.8	< 0.01	6.3	2.2	< 0.01

Therefore, we compared the severity of each item of the questionnaire among the three categories and performed subgroup analysis to see an interaction between the two variables with treating time since surgery as a categorical variable.

Severity of each item of the questionnaire

We compared the severity of each item of the questionnaire among the three categories of the time since surgery to identify items that were severe in each category. Nearly half of the 40 items significantly

differed among the three groups, as indicated by the Kruskal-Wallis test (Supplementary Table 2). The severity of these symptoms was more severe in a shorter time since surgery.

Next, we compared the severity of each item of the questionnaire among the three cancer types to identify items that were severe in each cancer type. More than half of the 40 items significantly differed among the three groups, as indicated by the Kruskal-Wallis test (Supplementary Table 3). Patients with ovarian cancer had more severe hot flushes, sweat, back pain, numbness, dull sense of hands and feet, vaginal discharge, and vaginal dryness than those with endometrial cancer, as assessed by chi-squared test. Patients with cervical cancer had more severe hot flushes, sweat, cold constitution, shoulder stiffness, irritability, nervousness, anxiety, headaches, depression, loss of volition, wakefulness, nausea, eye dryness, and abdominal distension than those with endometrial cancer. In contrast, patients with endometrial cancer only had more severe hair loss than patients with cervical cancer.

Interaction between the time elapsed since surgery and cancer type

Patients were divided into three subgroups according to cancer type (Fig. 3A-C). In patients with endometrial cancer, symptom severity decreased with time, reaching its lowest at > 5 years after surgery (Fig. 3A). In patients with ovarian cancer, symptom severity was also the lowest at > 5 years after surgery (Fig. 3B). In contrast, in patients with cervical cancer, symptom severity remained unchanged over time (Fig. 3C).

Patients were divided into three subgroups according to the time elapsed since surgery (Fig. 3D-F). In all three subgroups, patients with endometrial cancer had lower symptom severity than those with ovarian or cervical cancer. In patients who had undergone surgery < 1 year previously, there were no differences among the cancer type groups (Fig. 3D). Among patients for whom 1–5 years had elapsed since surgery, those with endometrial cancer showed lower symptom severity than did those with ovarian or cervical cancer; however, there were no differences between the ovarian and cervical cancer groups (Fig. 3E). Among patients who had undergone surgery > 5 years previously, those with endometrial or ovarian cancer showed lower symptom severity than did those with cervical cancer (Fig. 3F).

When we compared the severity of each item of the questionnaire, we found a significant difference in the severity of only two symptoms, readily excitable and numbness, among cancer types in the subgroup of patients who had undergone surgery < 1 year previously. However, we found significant differences in the severity of many more symptoms (i.e., hot flushes, shoulder stiffness, irritability, nervousness, depression, loss of volition, vertigo, and vaginal discharge) in the subgroups of patients for whom 1–5 years and > 5 years had elapsed since surgery (Supplementary Table 4).

Discussion

In this study, we compared the severity of climacteric symptoms after surgery and adjuvant therapy among different groups of gynecological cancer survivors. Symptom severity decreased with time since

surgery in patients with endometrial or ovarian cancer. Patients with cervical cancer showed greater symptom severity compared with those with endometrial or ovarian cancer, and their symptoms' severity showed no change over time.

In this study, the severity of climacteric symptoms decreased with the time elapsed since surgery in patients with endometrial and ovarian cancer. This is consistent with a previous study that reported improvements in the QOL and mood of patients with gynecological cancer at 1 year after treatment [22]. However, two other studies showed that the treatment method, cancer stage, and time since cancer diagnosis are not correlated with QOL or mood [23] and that QOL after treatment is not improved at 2 years after surgery when comparing patients with gynecological cancer [24]. In contrast to symptom severity in patients with endometrial and ovarian cancer in our study, that in patients with cervical cancer remained unchanged over time. The severity of mental symptoms, such as depression and loss of volition, was higher in patients with cervical cancer than in those with endometrial and ovarian cancer regardless of the time elapsed since surgery. In agreement, a study showed that, in patients with cervical cancer, the QOL does not reach that of healthy individuals, not even at 2 years after surgery [25]. Therefore, the type of gynecological cancer, rather than the time elapsed since surgery, has a major effect on these differences.

Gynecological cancer survivors who are young and/or have undergone chemotherapy have lower QOL than those treated surgically [24]. Indeed, in this study, patients with cervical cancer were younger at initial consultation than those with ovarian or endometrial cancer, where age at first consultation positively correlated with time since surgery. For example, we compared patients with cervical cancer with those with endometrial cancer using chi-squared test and adjusted the results with age at first consultation categorized in three groups (< 45, 45–55, and > 55 years) using the Cochrane-Mantel-Haenszel test. We found that the severity of several symptoms, such as shoulder stiffness and wakefulness (Supplementary Table 5), was still higher in patients with cervical cancer.

Patients with gynecological cancer and healthy individuals were shown to have similar QOL, health, psychological health, socioeconomic status, and family status [7]. However, particularly those with cervical cancer have lower mental and physical HRQOL than do those with other cancer types [6]. Moreover, these patients have worse anxiety, depression, anger, and confusion levels than do those with endometrial cancer [23], even though the latter report markedly more negative mood than do healthy individuals [24]. Our results indicated that vasomotor symptoms were more severe in patients with cervical or ovarian cancer than with endometrial cancer, while mental symptoms such as irritability, nervousness, anxiety, depression, loss of volition, and wakefulness were more severe in those with cervical cancer than in those with endometrial cancer. The questionnaire in this study covered both mental and physical parameters of climacteric symptoms, but mental symptoms were not more severe in those with any cancer type when summing up the degree of symptom scores with regard to mental or physical parameters (Supplementary Table 6). The present study results demonstrate the importance of climacteric symptoms in evaluating the QOL and well-being of gynecological cancer survivors, and especially of cervical cancer survivors, although further studies are needed to confirm our findings.

This study had certain limitations. First, the study was performed at a single institution. Second, there was no control group without cancer diagnosis, and we could not compare the symptom severity with those without gynecological cancer. Third, we did not investigate differences in the socioeconomic background of patients. QOL, mood, and mental health are considered to be significantly associated with education, income, presence or absence of a partner, etc. [23]. Numerous studies have compared climacteric symptoms after cancer treatment and adjuvant therapy across different socioeconomic strata [6], and socioeconomic background can present risks for menopausal symptoms [26]. In Japan, it is often difficult to ask patients about their socioeconomic status. In a previous study, we intended to ask subjects about their socioeconomic status; however, that plan had been rejected by the Ethics Committee. Moreover, there are differences between Japan and other countries with respect to healthcare information and social background. Thus, more studies are required to include these factors. Fourth, we did not classify patients with respect to cancer stage. Although several reports have addressed the relationship between the QOL of patients with gynecological cancer and cancer stage, their results are inconsistent [27–29], and further studies are needed to address this issue. Fifth, some of the patients in this study were enrolled more than 20 years ago, and it is possible that surgical advances in the past two decades have resulted in improvements in postoperative symptoms [30]. Therefore, we also did not classify patients with respect to operational procedure on hysterectomy. There are several procedures that might affect post-surgical QOL, viz., simple (sometimes extended), semi-radical, and radical hysterectomy. Surgical procedures have improved significantly so we decided that it was difficult to use procedures as an independent variable. Finally, this study was cross-sectional; thus, changes in patients' symptoms during the course of the study are unknown.

Conclusions

Patients with cervical cancer showed more severe climacteric symptoms than did patients with endometrial or ovarian cancer. Overall, symptom severity decreased with the increasing time elapsed since surgery. However, in patients with cervical cancer, symptom severity did not change significantly with the time elapsed since surgery. Patients with cervical cancer may require more prompt intervention, including symptomatic treatment and longer follow-up, than do patients with endometrial or ovarian cancer.

Abbreviations

QOL
quality of life
HRQOL
health-related quality of life

Declarations

Ethics approval and consent to participate

All procedures performed in the studies involving human subjects were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All registered subjects provided written informed consent, and the study design was approved by the institutional review board at Keio University School of Medicine (approval no. 20140189).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study received no funding.

Authors' contributions

YH had full access to the clinical data used in this study and takes responsibility for the data's integrity and the accuracy of the data analysis. TY assisted in data analysis. YH and TY wrote a draft of this manuscript. YH, MY, TI, and DA participated in designing the study and collecting clinical data. TI, MM, KW, and DA reviewed a draft of this manuscript, and made comments. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

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Figures

Figure 1

Exclusion flow chart We initially registered 780 patients. After excluding 255 patients, we finally included 525 patients in the analysis.

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Figure 2

Climacteric symptom severity by time since surgery or cancer type Overall, symptom severity decreased as the time elapsed since surgery increased (A). Symptom severity was higher in patients with ovarian and cervical cancer (B). Y axis shows symptom severity. The lower (Q1) and upper (Q3) quartile of the box represent observations of the 25 and 75 percentiles, respectively. The diagram also shows the median (horizontal bar in the box) and mean (x in the box) observation. The whiskers extend up from the top of the box to the largest data element that is less than or equal to 1.5 times the interquartile range (IQR) and down from the bottom of the box to the smallest data element that is larger than 1.5 times the IQR. Values outside this range are considered to be outliers and are represented by dots. EC, endometrial cancer; OC, ovarian cancer; CC, cervical cancer

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Figure 3

Climacteric symptom severity by time since surgery and cancer type In patients with endometrial cancer (A) or ovarian cancer (B), symptom severity decreased with time after surgery. Even at 5 years after surgery, symptom severity was not changed in patients with cervical cancer (C). Patients with endometrial cancer in all subgroups according to time since surgery, and especially those in whom 1 or more years had passed since surgery, had less severe symptoms than those with ovarian or cervical cancer did (D-F). The Y axis shows symptom severity. The lower (Q1) and upper (Q3) quartile of the box represent observations of the 25 and 75 percentiles, respectively. The diagram also shows the median (horizontal bar in the box) and mean (x in the box) observation. The whiskers extend up from the top of the box to the largest data element that is less than or equal to 1.5 times the interquartile range (IQR) and down from the bottom of the box to the smallest data element that is larger than 1.5 times the IQR. Values outside this range are considered to be outliers and are represented by dots. EC, endometrial cancer; OC, ovarian cancer; CC, cervical cancer

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Supplementary Files

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