Pathological characteristics of ovarian cancer occurring after hysterectomy

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Summary

Objective: The aim of the current study was to examine the pathological characteristics of ovarian cancer occurring in women with previous hysterectomy.

Methods: Newly diagnosed cases of ovarian primary epithelial or primary peritoneal cancer, operated on in our department between January 2000 and December 2002, were included in this retrospective study. The patients were divided into two groups, group I included eight patients with ovarian cancer and previous hysterectomy, and group II comprised 70 patients with ovarian or primary peritoneal cancer, but without previous hysterectomy.

Results: There was no significant difference between the eight patients with ovarian cancer and previous hysterectomy and the 70 patients without previous hysterectomy considering the patients' characteristics. Conversely, there was a difference between the two study groups regarding the histology of the tumor, its grade and the stage of the disease. All patients with ovarian cancer and previous hysterectomy had poorly differentiated mixed epithelial or undifferentiated tumors. Nevertheless, only 25% of these patients were diagnosed in Stage IIIC.

Conclusion: It seems that besides reducing the risk of further ovarian cancer, hysterectomy also causes a change in the main histological sub-group of ovarian cancer, that develops in patients with previous hysterectomy. The greatest protective effect was observed for serous ovarian tumors.

Key words: Ovarian cancer; Primary peritoneal cancer; Hysterectomy; Pathological characteristics.

Introduction

Multiple studies have suggested that tubal ligation or hysterectomy (even without removal of ovaries) may protect against ovarian cancer [1-7]. There have been several hypothesized theories for this observation, including a screening effect [6, 8], blockage of particles coming into contact with the ovaries [9, 10], a decrease in the blood supply to the ovaries [2, 11] and a decrease in uterine growth factors that may be involved in ovarian cancer development [1].

Epithelial ovarian tumors are derived from the surface epithelium and typically constitute 80-90% of ovarian malignancies. Of the epithelial tumors, approximately 15% are of borderline malignant potential, while the rest are invasive cancers. There are several histopathological sub-groups of epithelial ovarian cancers [12]. In an English case-control study the epithelial ovarian cancers were distributed as follows: serous adenocarcinoma (43%), mucinous adenocarcinoma (15%), endometrioid adenocarcinoma (22%), clear cell adenocarcinoma (5%) and mixed or undifferentiated tumors (14%) [13]. Similar results have been reported in a Norwegian project (14).

The aim of the current study was to examine the prevalence of different histopathologic types of ovarian cancer, their grade of differentiation and the stage of the disease found in women with previous hysterectomy, and to compare the histopathologic features of these ovarian cancers with those characterizing the ovarian cancers occurring in women without previous hysterectomy.

Material and Methods

Newly diagnosed cases of ovarian primary epithelial or primary peritoneal cancer, operated on in our department between January 2000 and December 2002, were included in this retrospective study. Tissue diagnosis was established by the same pathologist (S.Z). Cases diagnosed as borderline tumors were not included in this study, thus only true malignant cases were included.

Medical records were used for all relevant data. The patients were divided into two groups, group I included only patients with previous hysterectomy – eight patients with ovarian cancer and one patient with primary mesothelioma, group II consisted of 70 patients with ovarian or primary peritoneal cancer, but without previous hysterectomy.

All cases were histologically typed according to the World Health Organization classification [15], and were staged using the criteria established in 1987 by the International Federation of Gynecology and Obstetrics (FIGO) [16].

Statistical analysis was performed using the Student's t-test for comparison of mean values and the chi-square test for comparison of proportions. A result of $p < 0.05$ was considered to be significant.

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Results

The percentage of patients admitted to our department with ovarian cancer and previous hysterectomy constituted 12.5% of all cases with malignant ovarian or primary peritoneal cancer operated on in our department throughout the period January 2000 to December 2002.

There was no significant difference between the eight patients with ovarian cancer and previous hysterectomy and the 70 patients without previous hysterectomy considering the age of the patients, gravidity, parity and menarche (Table 1). There was also no difference between the two groups comparing the percentage of patients with a second primary or with familial cancer, as well as no difference comparing the percentage of smokers or oral contraceptive users.

Conversely, there was a difference between the two study groups regarding the histology of the tumor, its grade and the stage of the disease (Table 2). All the patients presenting with ovarian cancer and previous hysterectomy had either mixed epithelial tumors (4 patients) or undifferentiated tumors (4 patients). Conversely, the group of patients without previous hysterectomy demonstrated serous papillary tumors (42.8% of cases), mixed epithelial (22.8%), endometrioid (17.1%) and primary peritoneal tumors (17.1%). There was also a significant difference between the two groups of patients regarding the grade of the tumor ($p = 0.01$). While all eight patients with previous hysterectomy demonstrated poorly differentiated tumors, the group of patients without previous hysterectomy presented only 57.1% of poorly differentiated tumors. There was also a significant difference between the two study groups relating to the stage of the disease ($p < 0.05$). Only 25% of patients with ovarian cancer and previous hysterectomy as compared with 60% of women with ovarian cancer but without previous hysterectomy, were diagnosed in Stage IIIC. On the other hand, the percentage of cases undergoing optimal debulking, as well as the median level of CA-125, did not differ significantly comparing the two study groups (Table 2).

Table 1.

Patient characteristics	Group I (with previous hysterectomy) n = 8	Group II (without previous hysterectomy) n = 70	Significance p
Mean age (yrs)	61.0 ± 9.8	60.4 ± 12.7	NS[a]
Menarche (yrs)	13.0 ± 0.2	13.6 ± 1.3	NS
Gravidity (no.)	1.7 ± 1.5	3.3 ± 2.6	NS
Parity (no.)	1.8 ± 1.6	2.3 ± 2.0	NS
Second primary cancer (%)	25.0	17.1	NS
Familial cancer (%)	75.0	42.8	NS
Smoking (%)	15.0	17.1	NS
Use of oral contraceptives (%)	0	8.5	NS

[a]NS: non significant.

Table 2.

Tumor characteristics	Group I (with previous hysterectomy) n = 8	Group II (without previous hysterectomy) n = 70	Significance p
Histology			
– Serous papillary (%)	0	42.8	0.01
– Endometrioid (%)	0	17.1	NS[a]
– Mixed epithelial (%)	50.0	22.8	NS
– Undifferentiated (%)	50.0	0	0.0001
– Primary peritoneal (%)	0	17.1	NS
Grade			
– Poorly differentiated (%)	100	57.1	0.01
– Other grades (%)	0	42.9	
Stage IIIC (% of cases)	25.0	60.0	0.05
Optimal debulking (%)	75	80.0	NS
Median level of CA-125 (IU/ml)	84	1141	NS

[a]NS: non significant.

Discussion

The issue of ovarian cancer appearing in patients with previous hysterectomy has been previously reported [1-7, 17-22]. Although the occurrence of reduced risk of ovarian cancer following tubal ligation or hysterectomy has been quite well established [1-7, 17-22], the characteristics of ovarian cancer occurring in patients with previous hysterectomy has not been well studied. In this retrospective study, we tried to assess whether there was any effect of previous hysterectomy on characteristics of further appearing ovarian cancer, as compared to patients presenting with ovarian cancer and without previous hysterectomy.

According to our data, there were no cases of primary peritoneal carcinoma nor cases of serous papillary ovarian cancer in the group of patients who had undergone hysterectomy before developing ovarian cancer, whereas the group of patients with ovarian cancer and without previous hysterectomy comprised 17.1% cases of primary peritoneal carcinoma and 42.8% serous papillary ovarian cancer cases. On the other hand, the patients with previous hysterectomy presented with undifferentiated (50% of cases) and mixed epithelial (50% of cases) ovarian cancer, whereas the group of patients without hysterectomy contained only 22.8% of mixed epithelial ovarian cancer and no case of undifferentiated ovarian carcinoma. Although our study group was quite small (only 8 patients), we can still observe a significant reduction in the incidence of serous papillary ovarian cancer cases, as well as a reduction in the histological subgroups of primary peritoneal and endometrioid tumors. Perhaps an addition of more cases to the study group would demonstrate a more significant reduction in the incidence of these histological sub-groups. It is interesting to mention the only case of what seemed at the beginning to be primary peritoneal carcinoma in a patient with previous hysterectomy and right salpingo-oophorectomy, that turned out to be primary malignant mesothelioma. Thus, our results are in agreement with previous publications demonstrating a reduced risk of developing serous ovarian and primary peritoneal cancers [3], as well as endometrioid ovarian cancer [19] in patients with previous surgical tubal occlusion. We found no effect on mucinous tumors, as has been demonstrated by Cramer and Xu [1], because there was no such histological sub-group in either of the groups in the current study. The difference

between our study and the above quoted studies refers to patients after previous hysterectomy (in our study) versus patients after tubal sterilization (in previous publications). The current study supports the previously proposed theory by Cramer and Xu [1], suggesting the involvement of uterine growth factors in ovarian cancer pathogenesis. According to this theory, hysterectomy obviously removes the source of uterine growth factors, while interrupted uteroovarian circulation after tubal ligation reduces the concentration of growth factors that reaches the ovaries directly from the uterus [1]. An alternate explanation for the reduced risk in ovarian cancer after hysterectomy or tubal ligation can be an interrupted retrograde transport of potential exogenous carcinogens through the Fallopian tubes into the intraperitoneal cavity [1, 18]. This explanation gains support in the high frequency of retrograde menstrual flow [23].

We suggest a theory that the existence of a uterus and potential uterine growth factors might be necessary for the development of primary peritoneal carcinoma, a cancer which does not exist in males. This is an interesting issue which should be further researched.

Another observation in the current study was that all ovarian cancer cases in patients with previous hysterectomy were poorly differentiated (grade 3), while the group of patients without previous hysterectomy demonstarted only 57.1% of cases, diagnosed as grade 3. Yet, the stage of the disease was more advanced in patients without previous hysterectomy, being Stage IIIC in 60% of women, while the group of patients with previous hysterectomy demonstrated only 25% of cases in Stage IIIC. We cannot provide an explanation for this discrepancy. However, with regard to the poor differentiation of these tumors, we could quote the publication of Naik *et al.*, [24], proposing a theory that ovarian cancers which continue to develop despite the protective effect of the sterilization procedure, probably have a different etiological pathway (an adverse genetic predisposition?) and a relatively poorer prognosis [24]. The possible protective effect of years passing after hysterectomy on the stage of the disease cannot be regarded in the current study because of too small number of cases in the study group.

The lower, although not significantly different, median level of CA-125 in the group of patients with ovarian cancer and previous hysterectomy probably reflects the lower percentage of serous tumors in this group, and not the favorable outcome.

In conclusion, it seems that besides reducing the risk of further ovarian cancer, the hysterectomy procedure also causes a change in the main histological sub-group of ovarian cancer that develops in patients with previous hysterectomy. The greatest protective effect of prior hysterectomy was observed in serous ovarian tumors. Further studies are indicated to confirm the present results.

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