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Prior Tubal Ligation Might Influence Metastatic Spread of Nonendometrioid Endometrial Carcinoma

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Objective: The exfoliation of endometrial carcinoma might intraperitoneally spread through the fallopian tube. We analyzed the influence of prior tubal ligation (TL) in endometrial carcinoma to evaluate whether it can prevent the process and improve patients' survival.

Methods: A total of 562 patients with a diagnosis of endometrial carcinoma at the Peking University People's Hospital between July 1995 and June 2012 were enrolled in this study. The patients were divided into 2 groups based on the presence or absence of prior TL. International Federation of Gynecology and Obstetrics stage distributions, recurrence rates, survival status, and histopathological findings were compared between the 2 groups. Kaplan-Meier estimates and log-rank tests were used to compare the survival status based on TL in the overall population and stratified by histopathological subtypes and International Federation of Gynecology and Obstetrics stages. Cox models analysis was used to estimate the hazard ratios and 95% confidence intervals for associations between TL and carcinoma-specific mortality. All statistical tests were 2-sided.

Results: Of the 562 patients, 482 (85.7%) had a diagnosis of endometrioid and 80 patients (14.2%) with nonendometrioid carcinoma. Tubal ligation was associated with negative peritoneal cytology in the total population ($P = 0.015$) and in patients with endometrioid carcinomas ($P = 0.02$) but not help to reduce carcinoma-specific mortality ($P = 0.095$ and $P = 0.277$, respectively). In the nonendometrioid group, TL was not only associated with negative peritoneal cytology ($P = 0.004$) but also with lower stage ($P < 0.001$) and lower recurrence rate ($P < 0.005$), resulting in improved prognosis ($P = 0.022$). In Cox models analysis adjusted for covariates, TL was inversely associated with lower endometrial carcinoma-specific mortality (hazard ratio, 0.47; 95% confidence interval, 0.14–2.6).

Conclusion: Tubal ligation was associated with lower positive peritoneal cytology, stages, and recurrence rate, and improved prognosis among patients with nonendometrioid carcinoma. Tubal ligation might influence metastatic spread of nonendometrioid endometrial carcinoma. It could also help to reduce positive peritoneal cytology among patients with endometrioid carcinoma, but lacked prognostic significance.

Key Words: Tubal ligation, Endometrial carcinoma, Nonendometrioid carcinoma

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Endometrial carcinoma could metastasize via lymphatic systems, blood vessels, and direct invasion to the uterine muscular layer, or by exfoliation through the fallopian tube into the peritoneal cavity; however, the clinical importance of the latter process remains unconfirmed.¹⁻⁷ Some researchers argued that the exfoliation of endometrial carcinoma cells, with retrograde passage via the fallopian tubes, was the most plausible route of tumor spread to the abdominal cavity.^{4,5,8,9} An analysis of 262 endometrial cancers including different tumor subtypes found that in 26.1% of high-grade endometrial cancers, tumor cells were identifiable within the fallopian tube lumen, whereas in the low-grade cases, it was only 2.8%.⁷ Therefore, whether the malignant tumor cells could easily split from the primary mass, travel retrograde through the fallopian tubes and finally form true metastases might differ between different histological subtypes.

The fallopian tube may represent an important passage to the peritoneal cavity for both true metastases and potentially inconsequential dislodgement of cells after medical interventions. Nonetheless, peritoneal cytology was recently removed from endometrial cancer staging guidelines,¹⁰ as it might lack independent overall prognostic significance, but it was still recorded as a separate risk factor for endometrial carcinomas.¹¹

We hypothesized that tubal ligation (TL) could block passage of exfoliative cells into the peritoneal cavity, along with lower stage and mortality. A report of 4489 endometrial carcinomas found that TL was inversely associated with stage III and IV carcinomas and peritoneal metastasis but showed no independent association with improved survival as it might affect mortality mainly through its effects on stages.¹² Another report of 142 serous endometrial carcinomas found that although positive peritoneal cytology and stage IV disease were less frequent among women with TL, TL was associated with worse prognosis attributable to increased nodal metastases.⁶ In the present study, we examined the associations between TL, peritoneal cytology, endometrial carcinoma stages, extrauterine metastasis, recurrence rate, and mortality in 562 patients with endometrial carcinoma including the strong predominant endometrioid carcinoma and other more aggressive subtypes (nonendometrioid carcinomas).

METHODS

Study Population

This retrospective study was approved by the institutional review board of the Peking University People's Hospital. Between July 1995 and June 2012. A total of 562 patients with endometrial carcinomas (carcinoma or carcinosarcoma) presenting for primary intervention and surgically managed at the Peking University People's Hospital were enrolled in this study. The patients had not undergone prior retroperitoneal surgery or pelvic/abdominal radiotherapy.

Among the 562 patients, 482 (85.8%) had a diagnosis of endometrioid carcinoma and 80 (14.23%) with nonendometrioid carcinomas including 40 serous carcinomas, 19 clear cell carcinomas, 18 carcinosarcomas, and 3 small cell carcinomas.

Treatment

All patients underwent hysterectomy, bilateral adnexectomy, and lymph node sampling. Cytoreductive surgery was performed for intra-abdominal disease.

The taxonomy proposed by the World Health Organization (WHO) was used for ascertaining histopathological subtypes.¹³ Definitive surgical staging was performed for adverse histological findings. Grading was determined according to the International Federation of Gynecology and Obstetrics (FIGO) criteria.¹⁴ The pathology review was conducted by gynecologic pathologists of the Peking University People's Hospital. Stage assignment was based on the 2009 FIGO staging classification.¹¹

Oral progestin therapy was mainly given based on the pathological results of endometrioid carcinoma with positive progesterone receptors (PR+). Medroxyprogesterone acetate was the main choice. The rationale for other adjuvant therapies was generally based on the presence of extrauterine disease identified via definitive surgical staging. In the absence of specific acceptable clinical trials, patients with extrauterine metastasis were offered chemotherapy alone or in combination with radiotherapy. Platinum-based combination chemotherapy with doxorubicin or paclitaxel was the treatment of choice.

Data Collection and Statistical Analysis

We mainly collected the clinical data from hospital records of the patients. Specifically, a surgical history of bilateral TL or its equivalent was identified by reviewing the records as it was commonly recorded in the menstrual obstetric history. One hundred thirteen patients (20.1%) presented with a history of TL, whereas 449 (79.9%) had no history of TL. Follow-up information on causes of death was available through June 2013. When outcome details were deemed insufficient, letters to patients or their physicians, telephone interviews, or a combination of these methods of communication were used. Finally, of the 562 patients enrolled, 495 (88.1%) completed the whole follow-up.

Statistical analyses were performed using the SPSS software (version 16.0). We analyzed the data of the overall population, and patients with endometrioid and nonendometrioid carcinomas. Distributions of age, body mass index, tumor subtypes (endometrioid and nonendometrioid), stages, grades, myometrial invasion, adnexal involvement, lymphovascular space invasion, parametrial involvement, pelvic and aortic lymph node involvement, peritoneal cytology, pelvic metastasis, recurrence rate, and adjuvant therapy (oral progestin therapy, radiotherapy, and chemotherapy) by TL status were compared by χ^2 tests. Follow-up duration was computed from the date of surgery to date of death or end of follow-up. Kaplan-Meier estimates and log-rank tests were used to compare survival status according to TL in the overall population and stratified by histopathological subtypes and FIGO stages including early stages (stages I-II) and late stages (stages III-IV) based on whether the tumors were confined to the uterus or not. Cox models analysis was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for relationships between TL and carcinoma-specific mortality.

TABLE 1. Tumor characteristics of the 562 patients with FIGO Stage I–IV endometrial carcinoma according to previous history of tubal ligation

Characteristics	Tubal Ligation, No. (%)		P*
	No (n = 449)	Yes (n = 113)	
Age at diagnosis, y			0.134
<50	112 (25)	20 (18)	
50–59	171 (38)	50 (44)	
60–69	110 (25)	34 (30)	
≥70	56 (12)	9 (8)	
BMI, kg/m ² †			0.291
<18.5	8 (2)	0 (0)	
18.5–24.9	136 (41)	36 (38)	
25.0–29.9	130 (40)	37 (39)	
≥30	55 (17)	21 (23)	
Histologic subtype			0.380
Endometrioid	388 (86)	94 (83)	
Nonendometrioid	61 (14)	19 (17)	
FIGO stages			0.597
I	318 (71)	80 (71)	
II	51 (11)	16 (14)	
III	62 (14)	15 (13)	
IV	18 (4)	2 (2)	
Grades‡			0.421
G1–2	327 (84)	76 (81)	
G3	61 (16)	18 (19)	
Myometrial invasion†			0.368
<1/2 layer	332 (74)	79 (70)	
≥1/2 layer	116 (26)	34 (30)	
PLN involvement‡			0.507
No	404 (90)	104 (92)	
Yes	45 (10)	9 (8)	
Peritoneal cytology†			<0.001*
Negative	324 (78)	107 (95)	
Positive	92 (22)	6 (5)	
LVSI			0.612
Negative	366 (82)	91 (81)	
Positive	83 (18)	22 (19)	
Adnexal involvement			0.824
Negative	416 (93)	104 (92)	
Positive	33 (7)	9 (8)	
Pelvic metastasis‡			0.217
Negative	430 (96)	111 (98)	
Positive	19 (4)	2 (2)	

TABLE 1. (Continued)

Characteristics	Tubal Ligation, No. (%)		P*
	No (n = 449)	Yes (n = 113)	
Parametrial involvement			0.388
Negative	429 (96)	110 (97)	
Positive	20 (4)	3 (3)	
Oral progestin therapy†			0.376
No	195 (46)	44 (41)	
Yes	230 (54)	63 (59)	
Chemotherapy‡			0.712
No	224 (52)	58 (54)	
Yes	205 (48)	49 (46)	
Radiotherapy‡			0.531
No	314 (73)	80 (76)	
Yes	115 (27)	25 (24)	
Recurrence‡			0.112
No	334 (85)	92 (91)	
Yes	59 (15)	9 (9)	

*P value was from 2-sided χ^2 test.
 †Missing values excluded.
 ‡Among women with other pelvic organs involved excluding uterus and bilateral adnexa.
 BMI, body mass index; LVSI, lymphovascular space invasion; PLN, pelvic lymph node.

All calculated P values were 2-sided, and P < 0.05 was considered statistically significant.

RESULTS

Study Population

Of the 562 patients, 20.1% (n = 113) presented a previous TL at a median age of 25 years (range, 2–51 years). Distributions of tumor characteristics according to TL status are shown in Table 1. Tubal ligation was associated with negative peritoneal cytology in the total population (P = 0.015) as well as the patients with endometrioid carcinoma (Table 2) (P = 0.02). However, in the nonendometrioid group, TL was not only associated with negative peritoneal cytology (P = 0.004) but also with lower stage (P < 0.001) and recurrence rate (P < 0.005) (Table 2).

Tubal Ligation and Mortality

Among the 562 endometrial carcinoma patients, 495 completed the follow-ups with a median follow-up of 5.34 years (range, 4 days to 21.34 years). Among the 63 deaths, 60 (95.2%) were ascribed to endometrial carcinoma. As compared to women with intact tubes, those with status post-TL had lower endometrial carcinoma-specific mortality among nonendometrioid carcinomas (log-rank P = 0.022). The

TABLE 2. Tumor characteristics of the patients with FIGO stage I to stage IV endometrioid (n = 482) and nonendometrioid (n = 80) carcinoma according to history of tubal ligation

Characteristics	Endometrioid Carcinoma (n = 482)			Nonendometrioid Carcinoma (n = 80)		
	Tubal Ligation, n (%)		P*	Tubal Ligation, No. (%)		P*
	No (n = 388)	Yes (n = 94)		No (n = 61)	Yes (n = 19)	
Age at diagnosis, y			0.313			0.102
<50	101 (26)	17 (18)		11 (18)	3 (16)	
50–59	153 (39)	45 (48)		18 (30)	5 (26)	
60–69	94 (24)	24 (26)		16 (26)	10 (53)	
≥70	40 (11)	8 (8)		16 (26)	1 (5)	
BMI, kg/m ² †			0.100			0.204
<18.5	6 (2)	0 (0)		2 (4)	0 (0)	
18.5–24.9	113 (40)	27 (34)		23 (46)	9 (64)	
25.0–29.9	116 (42)	32 (40)		14 (28)	5 (36)	
≥30	44 (16)	21 (26)		11 (22)	0 (0)	
FIGO stages			0.597			0.003*
I	284 (73)	71 (75)		34 (56)	9 (47)	
II	49 (13)	10 (11)		2 (3)	6 (31)	
III	45 (12)	13 (14)		17 (28)	2 (11)	
IV	10 (2)	0 (0)		8 (13)	2 (11)	
Grades†				No		
G1–2	327 (84)	76 (81)	0.421			
G3	61 (16)	18 (19)				
Myometrial invasion			0.399			0.786
<1/2 layer	289 (75)	66 (70)		43 (72)	13 (68)	
≥1/2 layer	99 (25)	28 (30)		17 (28)	6 (32)	
PLN involvement†			0.867			0.059
No	353 (91)	85 (90)		51 (84)	19 (100)	
Yes	35 (9)	9 (10)		10 (16)	0 (0)	
Peritoneal cytology†			0.001*			0.004*
Negative	292 (82)	90 (96)		32 (52)	17 (90)	
Positive	63 (18)	4 (4)		29 (48)	2 (10)	
LVSI			0.560			0.788
No	369 (95)	88 (94)		43 (70)	14 (74)	
Yes	19 (5)	6 (6)		18 (30)	5 (26)	
Adnexal involvement			0.486			0.422
Negative	370 (95)	88 (94)		46 (75)	16 (84)	
Positive	18 (5)	6 (6)		15 (25)	3 (16)	
Pelvic metastasis‡			0.136			0.532
Negative	379 (98)	94 (100)		51 (84)	17 (89)	
Positive	9 (2)	0 (0)		10 (16)	2 (11)	
Parametrial involvement			0.276			0.766
Negative	376 (97)	93 (99)		53 (87)	17 (89)	
Positive	12 (3)	1 (1)		8 (13)	2 (11)	

(Continued on next page)

TABLE 2. (Continued)

Characteristics	Endometrioid Carcinoma (n = 482)			Nonendometrioid Carcinoma (n = 80)		
	Tubal Ligation, n (%)		P*	Tubal Ligation, No. (%)		P*
	No (n = 388)	Yes (n = 94)		No (n = 61)	Yes (n = 19)	
Oral progestin therapy†			0.076	No		
No	149 (39)	26 (29)				
Yes	230 (61)	63 (71)				
Chemotherapy†			0.660			0.276
No	216 (57)	53 (60)		8 (16)	5 (28)	
Yes	163 (43)	36 (40)		42 (84)	13 (72)	
Radiotherapy†			0.536			0.946
No	273 (72)	67 (75)		41 (82)	13 (81)	
Yes	106 (28)	22 (25)		9 (18)	3 (19)	
Recurrence‡			0.493			0.003*
No	306 (90)	74 (92)		20 (44)	16 (84)	
Yes	34 (10)	6 (8)		25 (56)	3 (16)	

*P value was from 2-sided χ^2 test.

†Missing values excluded.

‡Among women with other pelvic organs involved excluding uterus and bilateral adnexa.

differences among the total population and endometrioid carcinoma cases were not statistically significant (Fig. 1). Associations between TL status and carcinoma-specific mortality within early stages (log-rank, $P = 0.240$) and late stages (log-rank, $P = 0.341$) did not show statistically significant differences.

Univariate regression analysis showed that TL was associated with endometrial carcinoma-specific mortality (HR, 0.27; 95% CI, 0.08–0.9) among nonendometrioid cases. However, Cox models adjusted for covariates demonstrated that TL was inversely unassociated with endometrial carcinoma-specific mortality (HR, 0.47; 95% CI, 0.14–2.6).

DISCUSSION

This study demonstrated that women with a history of TL and endometrial carcinoma presented with lower positive peritoneal cytology than those without TL, resulting in a similar prognosis. In contrast, a prior report of 4489 patients with endometrial carcinoma with a history of TL not only showed lower positive peritoneal cytology and lower-stage diseases but also better prognosis.¹² This is because the proportion (26.17%) of nonendometrioid carcinoma subtypes in that study was much higher than ours (14.29%), which might majorly influence the overall results. As the biological behaviors

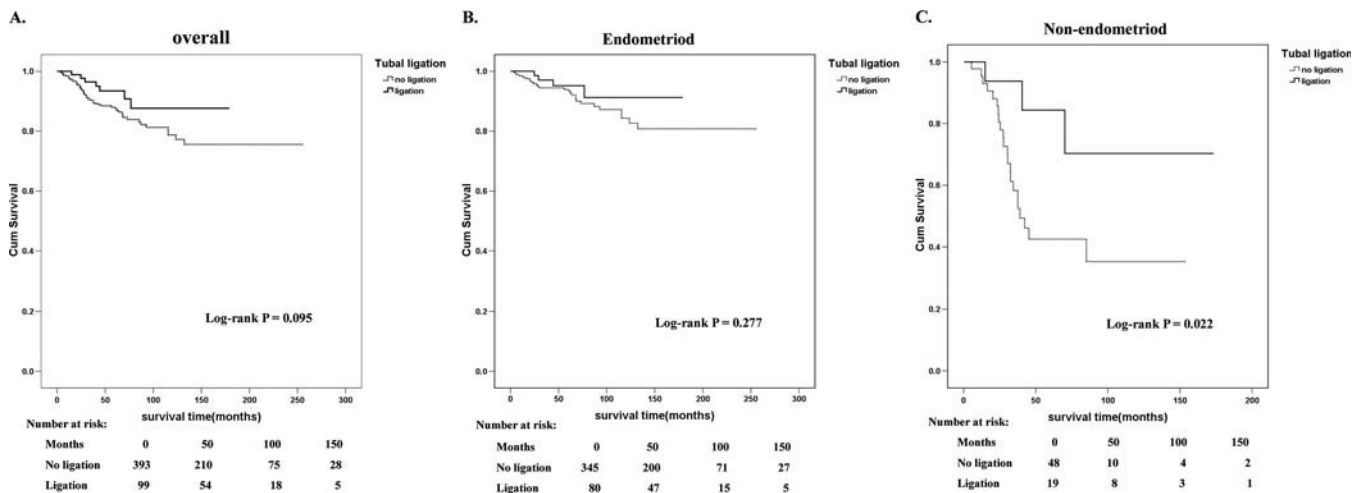


FIGURE 1. Endometrial carcinoma-specific mortality according to tubal ligation status in (A) overall population, (B) patients with endometrioid carcinomas, and (C) patients with non-endometrioid carcinomas.

between endometrioid and nonendometrioid carcinomas vary greatly, we have separately analyzed the influences of TL on each of them in the following discussion.

Among the patients with endometrioid carcinoma, those with a history of TL had lower positive peritoneal cytology but similar prognosis to the patients without TL. A previous meta-analysis concluded that hysteroscopy is associated with a statistically significant increase in positive peritoneal cytology, but not with worse prognosis, suggesting that uterine insufflation during the procedure may detach tumor cells that pass through the tubes and reach the peritoneal cavity without worsening clinical outcomes.¹⁰ This may be true for endometrioid carcinoma, as it is the most prevalent subtype of endometrial carcinoma with relatively benign biological behavior. Therefore, we inferred from our analysis that TL could block transtubal passage of endometrioid carcinoma cells into the peritoneal cavity, but this would not affect mortality, as these cells might lack the potential to implant and form peritoneal metastases. Nonendometrioid carcinoma subtypes, particularly serous carcinomas,¹⁵ may metastasize despite limited tumor volume in the uterus. Notably, another molecular analysis suggested that intrauterine and extrauterine tumor cells are often clonally related.^{16–19} In our study, unlike women with endometrioid carcinomas, women with a history of TL and nonendometrioid carcinoma had even lower positive peritoneal cytology, lower-stage diseases, and lower recurrence rate than those without TL, thus resulting in an improved prognosis, which was analogous to a prior report of 4489 endometrial carcinomas. Therefore, interruption of transtubal passage of tumor cells with aggressive metastatic potential is a possible explanation for the improved prognosis related to TL.¹² Our study indirectly confirmed that transtubal migration for peritoneal spread may be an important and common pathway for nonendometrioid tumor subtypes. The report of 4489 endometrial carcinomas indicated that TL was independently associated with improved survival mainly by reducing the stages.¹² Similarly, we also found that TL may indirectly help to improve the prognosis among patients with nonendometrioid carcinoma subtypes by directly influencing other risk factors. These factors remain unclear, and we will further analyze after accumulating more cases. Therefore, TL is a nonindependent protective factor for the prognosis of patients with nonendometrioid carcinomas.

In conclusion, TL was associated with lower positive peritoneal cytology, stage, and recurrence rate, and improved prognosis in patients with nonendometrioid endometrial carcinomas. Tubal ligation might influence metastatic spread of nonendometrioid endometrial carcinoma. Tubal ligation could help to prevent migration of exfoliated endometrioid carcinoma cells from the uterine cavity via fallopian tubes for intraperitoneal spread, leading to lower positive peritoneal washings, but lacks prognostic significance.

REFERENCES

- Mulvany NJ, Arnstein M, Ostör AG. Fallopian tube cytology: a histocorrelative study of 150 washings. *Diagn Cytopathol.* 1997;16:483–488.
- Arikan G, Reich O, Weiss U, et al. Are endometrial carcinoma cells disseminated at hysteroscopy functionally viable? *Gynecol Oncol.* 2001;83:221–226.
- Sherman ME, Bitterman P, Rosenshein NB, et al. Uterine serous carcinoma. A morphologically diverse neoplasm with unifying clinicopathologic features. *Am J Surg Pathol.* 1992;16:600–610.
- Soslow RA, Pirog E, Isacson C. Endometrial intraepithelial carcinoma with associated peritoneal carcinomatosis. *Am J Surg Pathol.* 2000;24:726–732.
- Snyder MJ, Bentley R, Robboy SJ. Transtubal spread of serous adenocarcinoma of the endometrium: an underrecognized mechanism of metastasis. *Int J Gynecol Pathol.* 2006;25:155–160.
- Ayeni TA, Bakkum-Gamez JN, Mariani A, et al. Impact of tubal ligation on routes of dissemination and overall survival in uterine serous carcinoma. *Gynecol Oncol.* 2013;128:71–76.
- Stewart CJ, Doherty DA, Havlat M, et al. Transtubal spread of endometrial carcinoma: correlation of intra-luminal tumour cells with tumour grade, peritoneal fluid cytology, and extra-uterine metastasis. *Pathology.* 2013;45:382–387.
- Jordan LB, Abdul-Kader M, Al-Nafussi A. Uterine serous papillary carcinoma: histopathologic changes within the female genital tract. *Int J Gynecol Cancer.* 2001;11:283–289.
- Zheng W, Xiang L, Fadare O, et al. A proposed model for endometrial serous carcinogenesis. *Am J Surg Pathol.* 2011;35:e1–e14.
- Chang YN, Zhang Y, Wang YJ, et al. Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis. *Fertil Steril.* 2011;96:957–961.
- Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Obstet.* 2009;105:103–104.
- Felix AS, Brinton LA, McMeekin DS, et al. Relationships of Tubal Ligation to Endometrial Carcinoma Stage and Mortality in the NRG Oncology/ Gynecologic Oncology Group 210 Trial. *J Natl Cancer Inst.* 2015;107:djv158.
- Scully RE, Bonfiglio TA, Kurman RJ, et al. Histological typing of female genital tract tumours. *World Health Organization International Histological Classification of Tumours.* 2nd ed. Berlin: Springer-Verlag; 1994:13–18.
- Creasman WT. Stages FIGO. 1988 Revision [announcements]. *Gynecol Oncol.* 1989;35:125–127.
- Fader AN, Starks D, Gehrig PA, et al. An updated clinicopathologic study of early-stage uterine papillary serous carcinoma (UPSC). *Gynecol Oncol.* 2009;115:244–248.
- Jia L, Yuan Z, Wang Y, et al. Primary sources of pelvic serous cancer in patients with endometrial intraepithelial carcinoma. *Mod Pathol.* 2015;28:118–127.
- Baergen RN, Warren CD, Isacson C, et al. Early uterine serous carcinoma: clonal origin of extrauterine disease. *Int J Gynecol Pathol.* 2001;20:214–219.
- Massuger L, Roelofsen T, Ham M, et al. The origin of serous ovarian cancer may be found in the uterus: a novel hypothesis. *Med Hypotheses.* 2010;74:859–861.
- Roelofsen T, van Kempen LC, van der Laak JA, et al. Concurrent endometrial intraepithelial carcinoma (EIC) and serous ovarian cancer: can EIC be seen as the precursor lesion? *Int J Gynecol Cancer.* 2012;22:457–464.