Estrogen therapy in patients with gynecologic cancer: a survey of gynecologists and oncologists in the United States

Jamie L. McDowell, DO,[1] Myla Strawderman, MS,[2] Sarah J. Betstadt, MD,[3] and Richard G. Moore, MD[1]

Abstract

Objective: Endometrial cancer (EC) and epithelial ovarian cancer (EOC) affect women of all ages, and the incidence of endometrial cancer in premenopausal women is rising. Menopause can be detrimental to longevity and quality of life, but evidence suggests estrogen therapy (ET) is safe in these patients. The purpose of this study was to evaluate the practice patterns of gynecologists and gynecologic oncologists (GYO) in the United States in regards to prescription of ET to gynecologic cancer patients. It was hypothesized that ET is underused in this population.

Methods: In 2024, a web-based survey was administered through email or postcard mailer to members of the Society of Gynecologic Oncology and the American College of Obstetricians and Gynecologists. Participants were asked demographic questions and whether they provide ET for patients with a history of EC, EOC, and cervical cancer.

Results: A total of 293 participants answered questions about at least one type of cancer. When asked if willing to provide ET, 63.82% (187/293) selected "yes" for EC, 65.19% (176/270) for EOC, and 96.8% (274/283) for cervical cancer. Due to lack of heterogeneity, cervical cancer was omitted from analysis. Gynecologic oncology providers were more likely than OBGYNs to prescribe ET for EC ($P = 0.0006$) and EOC patients ($P = 0.0009$). Those in practice for 10 or more years ($P = 0.022$), or who identified as male ($P = 0.019$), were more likely to prescribe ET to EC patients. Of those who do not prescribe ET, the most common reasons were belief that hormones are contraindicated, better options exist, and risk outweighs benefits. These options were selected more frequently by OBGYNs than GYOs.

Conclusion: Many gynecologists, and some gynecologic oncologists, are uncomfortable prescribing hormone therapy to patients with a history of endometrial or epithelial ovarian cancer, despite evidence suggesting its safety. This indicates a need for clinician education to ensure patients are counseled appropriately about options for treating menopausal symptoms.

Key Words: Endometrial cancer, Estrogen therapy, Ovarian cancer.

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A majority of gynecologic cancer patients are postmenopausal; however, it is estimated that 40% of patients are premenopausal or perimenopausal at diagnosis.[1] Many patients undergoing surgery for a gynecologic malignancy will require bilateral oophorectomy as part of their treatment. Women treated with chemotherapy and/or radiotherapy alone are also at risk of decreased ovarian function.[2] It is well established that surgical menopause before age 40 increases all-cause mortality, premature cognitive deterioration, and decreases quality of life, sexual function, and bone density.[3,4] Due to the increased efficacy of newer cancer therapies, it is important to consider the long-term effects of premature ovarian insufficiency and hormone deprivation in premenopausal gynecologic cancer patients. However, estrogen therapy (ET) is historically underused in this population, with many providers citing fear of cancer recurrence as the primary reason.[5-8]

In 2020, the Society of Gynecologic Oncology (SGO) released a statement to help guide the use of hormone therapy in gynecologic cancer patients, and it was affirmed by The Menopause Society (formerly The North American Menopause Society).[1] Currently, there are no publications that evaluate ET prescribing habits of gynecology practitioners in the United States for this population. We sought to explore and define the use of ET

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From the [1]Department of Gynecologic Oncology, Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY; [2]Department of Biostatistics and Computational Biology, University of Rochester, Rochester, NY; and [3]Department of OBGYN, University of Rochester Medical Center, Rochester, NY.

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Address correspondence to: Jamie L. McDowell, DO, 601 Elmwood Avenue, Rochester, NY 14642. E-mail: jamiemcdowell0@gmail.com.

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in women with a history of gynecologic cancer, and hypothesized that ET is underutilized in these patients.

METHODS

In November 2024, an IRB-approved, open, web-based Redcap survey was emailed to the Society of Gynecologic Oncology (SGO listserv) members. In addition, a postcard mailer displaying a survey QR code was sent to members of the American College of Obstetricians and Gynecologists (ACOG), inclusive only of those registered as OBGYN physicians and advanced practice practitioners (APP). ACOG members registered in an OBGYN subspecialty were excluded. The survey was active for 8 weeks; a total of 2 reminders were sent to the SGO listserv during this period. Additional mailers were not sent to ACOG members as postage was cost-prohibitive. The survey contained demographic questions about the respondents' sex identity, age group, years in practice, workplace setting, job title, and region of practice. Respondents were asked about practice patterns when prescribing hormone therapy to patients who had received definitive treatment for endometrial cancer (EC), epithelial ovarian cancer (EOC), and cervical cancer. The entire survey can be found in Supplemental Digital Content 1 (http://links.lww.com/MENO/B411). All survey takers were asked whether they were aware of the SGO statement about the use of ET in these populations, and whether its publication impacted their practice pattern. All responses were deidentified and stored in a secure and anonymous online database.

Statistics

The frequency and percentage of responses to each question were reported by type of cancer. Using χ^2 analysis, each demographic factor was assessed for the unadjusted association with the primary outcomes of whether or not they would prescribe ET within each cancer type. Principle findings are reported with 95% CI.

RESULTS

A total of 339 people initiated the survey and 293 completed prescribing questions about at least one type of cancer. Of the 293 respondents, 28 did not complete the demographics section, and an additional 7 withheld sex information. These 35 participants were still included in the analysis.

Endometrial cancer

All 293 respondents answered the question about providing estrogen therapy (ET) for EC patients; 63.82% (187/293) of respondents reported they do prescribe ET to this population. Prescribing patterns differed significantly based on sex, job title, and years in practice. Gynecologic oncology (GYO) attendings (78%, 95% CI = 71.0-85.9) and GYO advance practice practitioners (AP; 73%, 95% CI = 58.7-86.3) were the most comfortable, whereas OBGYN attendings (51%, 95% CI = 39.5-61.8) were the least comfortable ($P = 0.0006$). Those in practice for 10 or more years (73%, 95% CI = 66.2-80.7) were most likely to prescribe ET ($P = 0.022$), as well as those who identified as male (78%, 95% CI = 69.0-87.4, $P = 0.019$). There was no difference in prescribing based on practice setting or region (Table 1).

The influence of disease characteristics on prescription is shown in Table 2. Of the 187 who answered "yes," a majority of respondents only felt comfortable prescribing to patients with early-stage disease, grade 1 or 2 histology, age younger than 60 and only once symptomatic. Most respondents were comfortable providing both systemic and vaginal estrogen.

Of the 106 providers who do not prescribe estrogen to this population (36.2%, 95% CI = 30.7-41.7), the most frequently selected reasons were belief that potential risks outweighed the benefits (46%, 95% CI = 36.7-55.7), better treatment options exist (33%, 95% CI = 24.1-42.0), and/or that it is contraindicated (30%, 95% CI = 21.5-38.9). As seen in Table 4, these selections were made most frequently by general OBGYNs, however, some GYO providers also held these beliefs. When asked about their greatest concern, 86% (95% CI = 78.8-92.3) were worried about increasing the risk of recurrence of the previously treated cancer.

Epithelial ovarian cancer

A total of 270 respondents answered the question about prescribing ET to EOC patients, and 65.19% felt comfortable. Unlike for EC patients, only job title significantly impacted the likelihood of ET prescription ($P = 0.0009$) with 78% of GYO attendings prescribing (95% CI = 70.0-85.2). Difference in practice pattern varied based on sex and years of experience but did not reach significance. Prescribing choices were similar regardless of setting or region of practice (Table 1).

Respondents prescribe ET more often to patients younger than 60 years old, with advanced-stage disease, and to those with high-grade serous and mucinous tumors. Most respondents were comfortable providing both systemic and vaginal estrogen, but only when patients report menopausal symptoms (Table 3).

Ninety-four respondents do not prescribe estrogen to EOC patients (34.8%, 95% CI = 29.2-40.5). The most frequently selected reasons were belief that potential risks outweigh the benefits, and/or that it is contraindicated in this population. Once again, these selections were made by more general OBGYNs than GYOs. Providers' greatest concern was increasing the risk of recurrence (68%), but more providers cited thrombosis risk as a concern than in EC (15% vs 5%; Table 4).

Cervical cancer

Of the 283 respondents who answered this question, 96.8% were comfortable prescribing ET for cervical cancer patients. Due to the lack of heterogeneity, the differences in prescriber characteristics were not analyzed.

Alternative therapies

Respondents were also given the opportunity to select their preferred ET alternatives. Selective serotonin reuptake inhibitors (SSRIs) were the most frequently

TABLE 1. Characteristics of respondents who would prescribe ET by type of cancer patient

	Endometrial			Ovarian		
	N	Yes[a]	*P*[b]	N	Yes[a]	*P*[b]
Overall	293	187 (64)	—	270	176 (65)	—
Sex						
Male	78	61 (78)	0.019	78	58 (74)	0.055
Female	180	114 (63)	—	179	111 (62)	—
No response	35	—	—	13		—
Job title						
OBGYN APP	5	3 (60)	0.0006	5	2 (40)	0.0009
OBGYN attending	77	39 (51)	—	77	38 (49)	—
GYO APP	40	29 (73)	—	39	23 (59)	—
GYO fellow	27	14 (52)	—	27	19 (70)	—
GYO attending	116	91 (78)	—	116	90 (78)	—
No response	28	—	—	6	—	—
Years in practice (y)						
Still in training	27	14 (52)	0.022	27	19 (70)	0.091
1-9	94	56 (60)	—	94	53 (56)	—
10+	143	105 (73)	—	142	99 (70)	—
No response	29	—	—	7	—	—
Practice setting						
Trainees	203	135 (67)	0.957	202	136 (67)	0.181
No trainees	62	41 (66)	—	62	36 (58)	—
No response	28	—	—	6	—	—
Region						
NE	72	49 (68)	0.927	71	46 (65)	0.980
South	69	47 (68)	—	69	44 (64)	—
West	67	44 (66)	—	67	45 (67)	—
Midwest	57	36 (63)	—	57	37 (65)	—
No response	28	—	—	6	—	—

APP, advanced practice practitioner; ET, estrogen therapy; GYO, gynecologic oncologist; NE, northeast; OBGYN, obstetrician and gynecologist.

[a]The frequency (%) reporting they would prescribe ET.

[b]χ^2 test is used to compare the proportions prescribing ET between levels of each characteristic. Providers who did not provide a response are excluded.

TABLE 2. Influence of disease characteristics on prescription of ET for endometrial cancer patients

ET in endometrial cancer (N = 187)	
	Frequency (%)
Highest stage[a]	
1	108 (58)
2	54 (29)
3	3 (2)
4	22 (12)
Histology[b]	
Grade 1 endometrioid	183 (98)
Grade 2 endometrioid	112 (60)
Grade 3 endometrioid	55 (29)
Serous papillary	63 (39)
Clear cell	52 (28)
Highest age group[a]	
< 50	59 (32)
50-60	78 (42)
> 60	49 (26)
No response	1
Timing of treatment	
Immediately after surgery	46 (25)
Only if symptomatic	157 (84)
After adjuvant treatment	65 (35)
Formulation[b]	
Systemic only	19 (10)
Vaginal only	29 (16)
Both systemic/vaginal	139 (74)

ET, estrogen therapy.

[a]These answer choices were "select all that apply." These data show the highest stage or age group that respondents chose; eg, if a participant chose stages 1-3, the stage 3 selection is reflected in this table.

[b]These answer choices were "select all that apply."

selected (88.4%), followed by gabapentin (58%), and neurokinin-3 antagonists (46.4%). Phytoestrogens or clonidine were infrequently selected (10.24% and 19.80%).

Society of gynecologic oncology statement awareness

Of 293 providers who gave any information about prescribing ET, 267 responded to the question regarding the SGO statement. Of these, 158 (59%, 95% CI = 53.3-65.1) were aware of the SGO statement published in 2020. Of those who were aware, 72 (46%, 95% CI = 37.8-53.3) made a change in prescribing practice after its publication. One hundred nine providers were not aware of the SGO statement. Despite unawareness of the publication, 56 providers (51%) already prescribe ET for endometrial cancer patients and 58 (53%) prescribe ET for ovarian cancer patients.

DISCUSSION

The results of this survey suggest that many OBGYNs and some gynecologic oncologists do not have a favorable attitude towards prescription of ET to patients with a history of EC or EOC. Those more likely to prescribe ET to EC patients are male, specialized in gynecologic oncology, and/or have been in practice for > 10 years. Clinician specialty was the only significant characteristic to impact prescription of ET for EOC patients. The most common reason for not prescribing ET was a belief that the risks outweighed the benefits. In addition, many providers believe estrogen therapy is contraindicated and/or they are uncomfortable providing adequate medication counseling.

The decision to prescribe hormone therapy to patients with a history of gynecologic cancer is complex and sometimes controversial. Many patients choose to alternate surveillance visits with their primary OBGYN and GYO, and can sometimes transition care to their OBGYN 5 years after completing treatment. As indicated by our results and others, many gynecology providers, including some GYOs, still believe ET is contraindicated in EC and EOC patients. However, as outlined in the SGO statement, there is evidence that ET is safe in patients with early-stage disease (stages I-II).[1] In 2006, there was a randomized, double-blinded trial of ET versus placebo in patients who underwent surgery for stage I or II EC. The purpose of this study was to determine the effect of ET on recurrence rate and survival. Unfortunately, it was closed prematurely due to decreased enrollment after publication of the Women's Health Initiative (WHI). Despite this, 1,236 patients were available for analysis, and cancer recurrence rates were similar in the placebo and estrogen groups (1.9% vs 2.3%) after a median follow-up time of 35.7 months.[9] Similar findings are reported in multiple

TABLE 3. Influence of disease characteristics on prescription of ET for ovarian cancer patients

ET in ovarian cancer (N = 176)	
	Frequency (%)
Highest stage[a]	
1	33 (19)
2	24 (14)
3	11 (6)
4	107 (61)
No response	1
Histology[b]	
High-grade serous	162 (92)
Endometrioid	55 (31)
Clear cell	117 (66)
Mucinous	153 (87)
Highest age group[a]	
< 50	59 (34)
50-60	74 (43)
> 60	40 (23)
No response	3
Timing of treatment	
Immediately after surgery	67 (38)
Only if symptomatic	144 (82)
After adjuvant treatment	70 (40)
Formulation[b]	
Systemic only	24 (14)
Vaginal only	18 (10)
Both systemic/vaginal	133 (76)
No response	1

ET, estrogen therapy.
[a]These answer choices were "select all that apply." These data show the highest stage or age group that respondents chose; eg, if a participant chose stages 1-3, the stage 3 selection is reflected in this table.
[b]These answer choices were "select all that apply."

retrospective studies, all of which suggest no increased risk of disease recurrence with estrogen use.[10] This data points to the safety of ET in early-stage endometrial cancer patients and should be presented to all eligible patients for informed decision making.

Unlike endometrial cancer, where the incidence in younger patients is increasing,[11] EOC primarily affects postmenopausal women. However, studies estimate as many as 17% of patients are under 40 years of age at time of diagnosis.[12] Multiple prospective studies have suggested estrogen is not only safe but may also provide a survival advantage in these patients.[13-15] In addition, a meta-analysis published in 2018 concluded that exogenous hormone therapy does not have a negative effect on EOC overall survival or disease recurrence.[12] Despite these data, the results of our survey suggest there is still a significant number of providers who believe estrogen therapy is contraindicated in these patients.

The SGO does not endorse the use of systemic estrogen therapy in patients with advanced-stage endometrial cancer (stages III-IV) as there is little data regarding its safety. Similarly, there is a paucity of data regarding the safety of estrogen in patients with cancer subtypes likely to respond to antiestrogen therapy. These include uterine sarcoma and subtypes of EOC like low grade serous and endometrioid; estrogen therapy is not recommended in these patients.[1] Among the survey respondents who provide estrogen to EC or EOC patients, practice patterns were concordant with these recommendations. Specifically, in EC patients, most were only willing to prescribe to those with stage I or II disease. Some were comfortable providing estrogen to patients with stage III or IV disease, but it is possible these respondents included vaginal estrogen when making this selection. The majority of participants who provide ET to EOC patients were only comfortable prescribing to patients with high-grade serous, mucinous, and clear cell histologic subtypes.

Cervical cancer is not considered hormonally responsive and is not treated with antiestrogen medications, therefore, hormone therapy (HT) should be offered to these patients when indicated or desired.[1,2] Patients who retain their uterus and are treated with radiation should use combined estrogen and progesterone therapy to protect against the development of an endometrial malignancy.[1] Investigators in Sweden and Greece have reported that HT is underused in cervical cancer patients,[16,17] but there are little data evaluating this practice in the United States. Encouragingly, almost all respondents in our survey were comfortable providing HT to cervical cancer patients.

To the best of our knowledge, this is the first survey of its kind in the United States, but similar studies have been conducted in 5 other countries. In Belgium and Greece, generalist gynecologists were presented with a single vignette-style question about prescribing hormone therapy to a postmenopausal patient previously treated for low-risk endometrial cancer. In the Belgian study, respondents more frequently selected "yes" than in the Greece survey when asked about willingness to prescribe hormones (67% vs 30.4%). In the Greece survey, younger physicians working in an academic center were more likely to select yes, but in the Belgium survey, there was no difference in practice relative to age. Neither study showed a difference in practice relative to sex.[7,18]

Both generalist gynecologists and GYOs were assessed in surveys distributed in Germany, Japan, and Sweden.[5,8,19] All surveys asked about willingness to prescribe hormone therapy in the same patient scenarios: (1) a 41-year-old patient treated for stage IBG2 endometrial cancer, with moderate menopausal symptoms, and (2) a 38-year-old patient treated for stage IIIC1G3 endometrial cancer, with severe menopausal symptoms. The Japanese study also included 2 simple, hypothetical questions about willingness to prescribe to premenopausal and postmenopausal patients, independent of disease characteristics. The Swedish and German studies surveyed a larger number of benign gynecologists, whereas the Japanese study participants were mostly GYOs. In the German survey, respondents were asked whether estrogen was contraindicated in either patient scenario; 45.6% and 75.5% of respondents selected "yes" to the low and high-risk patients, respectively.[19] Responses were similar in the Swedish study, at 53.1% and 70.9% of generalist gynecologists, and 41.7% and 50% of GYOs.[5] Respondents from both surveys preferred the use of local estrogen over systemic therapy. In the Japanese survey, respondents were the most willing to prescribe systemic hormone therapy to all populations. In patients who were premenopausal with endometrial cancer at the time of surgery, 78% of providers felt comfortable, and in the postmenopausal group, this decreased to 49%. Nearly all providers would give systemic estrogen.[8] In all studies, the fear

TABLE 4. Reasons survey respondents do not prescribe ET to EC or EOC patients

	Endometrial (N = 106)	Ovarian (N = 94)
Reason for not prescribing ET[a]		
ET is contraindicated	32 (30)	28 (30)
Job title		
OBGYN attending	14 (44)	10 (36)
GYO APP	3 (9)	5 (18)
GYO fellow	6 (19)	3 (11)
GYO attending	4 (13)	9 (32)
Job title missing	5 (16)	1 (4)
Sex		
Male	4 (13)	7 (25)
Female	21 (66)	19 (68)
Sex missing	7 (22)	2 (7)
Years in practice (y)		
Still in training	6 (19)	3 (11)
1-9	9 (28)	12 (43)
10+	12 (38)	12 (43)
Duration missing	5 (16)	1 (4)
Risks outweigh benefits	49 (46)	43 (46)
Job title		
OBGYN attending	18 (37)	21 (49)
GYO APP	8 (16)	9 (21)
GYO fellow	6 (12)	4 (9)
GYO attending	12 (24)	8 (19)
Job title missing	5 (10)	1 (2)
Sex		
Male	7 (14)	9 (21)
Female	33 (67)	31 (72)
Sex missing	9 (18)	3 (7)
Years in practice (y)		
Still in training	6 (12)	4 (9)
1-9	19 (39)	15 (35)
10+	19 (39)	23 (53)
Duration missing	5 (10)	1 (2)
Uncomfortable counseling patients	21 (20)	32 (34)
Job title		
OBGYN APP	1 (5)	2 (6)
OBGYN attending	10 (48)	19 (59)
GYO APP	0	5 (16)
GYO fellow	2 (10)	2 (6)
GYO attending	2 (10)	4 (13)
Job title missing	6 (29)	0
Sex		
Male	5 (24)	6 (19)
Female	7 (33)	23 (72)
Sex missing	9 (43)	3 (9)
Years in practice (y)		
Still in training	2 (10)	2 (6)
1-9	7 (33)	18 (56)
10+	6 (29)	12 (38)
Duration missing	6 (29)	0
Better alternatives exist	35 (33)	22 (23)
Job title		
OBGYN APP	1 (3)	1 (5)
OBGYN attending	11 (31)	10 (45)
GYO APP	3 (9)	6 (27)
GYO fellow	6 (17)	2 (9)
GYO attending	13 (37)	3 (14)
Job title missing	1 (3)	0
Sex		
Male	10 (29)	7 (32)
Female	23 (66)	14 (64)
Sex missing	2 (6)	1 (5)
Years in practice (y)		
Still in training	6 (17)	2 (9)
1-9	14 (40)	10 (45)
10+	14 (40)	10 (45)
Duration missing	1 (3)	0
Other	NA	7 (7)
Greatest concern		
Increased risk of recurrence	89 (86)	63 (68)
Breast cancer risk	2 (2)	3 (3)
Thrombosis risk	5 (5)	14 (15)
Side effects	1 (1)	1 (1)
Other concern	7 (7)	7 (8)
No concerns	0	4 (4)
No response	2	2

APP, advanced practice ractitioner; EOC, epithelial ovarian cancer; EC, endometrial cancer; ET, estrogen therapy; GYO, gynecologic oncologist; OBGYN, obstetrician and gynecologist.

[a]These answer choices were "select all that apply."

of disease recurrence was the most commonly cited reason for not prescribing estrogen.

Willingness to prescribe hormone therapy to ovarian cancer patients was only evaluated in the Sweden and Greece surveys. Both surveys presented a hypothetical patient treated for low-risk ovarian cancer. In the Swedish study, 33.6% of generalist gynecologists thought estrogen was contraindicated, but none of the GYO respondents held this belief.[5] In the Greece survey, gynecologists were hesitant to prescribe estrogen, with only 48% responding "yes" when asked if comfortable.[20]

The number of responses to our survey was on par with similar published surveys. In addition, our survey was short and concise, which increased the likelihood of participants to complete all questions. However, we used broad questions rather than specific clinical vignettes, and this likely increased both the response and nonresponse bias. It is difficult to reflect the nuance of clinical decision-making with this type of questioning. The lower response rate of general OBGYN providers is likely because ACOG members were only reachable through postcard mailer, and no reminders were sent.

CONCLUSION

The consequences of menopause are clearly established and are detrimental to health and quality of life. However, it is evident from our survey and others alike that many gynecologists across the world still believe there is a contraindication to estrogen therapy in patients with a history of EC or EOC. Our data suggest that benign gynecology providers and those with less clinical experience are more likely to hold this misconception. As more premenopausal women are diagnosed with gynecologic cancer, it is imperative that clinicians are knowledgeable about who can safely receive estrogen therapy.

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