

# Lifestyle changes and the risk of developing endometrial and ovarian cancers: opportunities for prevention and management

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**Abstract:** Modifiable lifestyle factors, such as obesity, lack of physical activity, and smoking, contribute greatly to cancer and chronic disease morbidity and mortality worldwide. This review appraises recent evidence on modifiable lifestyle factors in the prevention of endometrial cancer (EC) and ovarian cancer (OC) as well as new evidence for lifestyle management of EC and OC survivors. For EC, obesity continues to be the strongest risk factor, while new evidence suggests that physical activity, oral contraceptive pills, and bariatric surgery may be protective against EC. Other medications, such as metformin and nonsteroidal anti-inflammatory drugs, may be protective, and interventional research is ongoing. For OC, we find increasing evidence to support the hypothesis that obesity and hormone replacement therapy increase the risk of developing OC. Oral contraceptive pills are protective against OC but are underutilized. Dietary factors such as the Mediterranean diet and alcohol consumption do not seem to affect the risk of either OC or EC. For EC and OC survivors, physical activity and weight loss are associated with improved quality of life. Small interventional trials show promise in increasing physical activity and weight maintenance for EC and OC survivors, although the impact on long-term health, including cancer recurrence and overall mortality, is unknown. Women's health providers should integrate counseling about these modifiable lifestyle factors into both the discussion of prevention for all women and the management of survivors of gynecologic cancers.

**Keywords:** lifestyle, prevention, endometrial cancer, ovarian cancer, gynecologic cancer, obesity

## Introduction

Obesity, inactivity, and poor diet contribute to ~20% of annual mortality worldwide.<sup>1</sup> Although tobacco consumption has historically driven lifestyle-related mortality, the epidemic of obesity (defined as body mass index [BMI]  $\geq 30$  kg/m<sup>2</sup>) and associated sedentary Western lifestyle has led to a rising incidence of obesity-related comorbidities and cancers in high-income countries since the 1980s.<sup>2</sup> Approximately half of all cancers are associated with modifiable risk factors.<sup>3</sup> In particular, cancers of the endometrium (uterine), breast, colon, prostate, and kidney are obesity driven.<sup>4</sup> A recent study suggested that, in the last decade, 25% of all cancers diagnosed worldwide could have been prevented if obesity rates had not increased.<sup>5</sup> Low- and middle-income countries are increasingly burdened by the obesity epidemic. The dangers of obesity and a sedentary lifestyle have become pervasive with a staggering 60% of adults globally (representing 3 billion people) expected to be overweight or obese by 2030.<sup>1,6</sup>

Among the most obesity-driven malignancies are the gynecologic cancers, particularly endometrial cancer (EC). The worldwide obesity epidemic may fuel an increase

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**Table 1** American Cancer Society recommendations for cancer prevention and survivorship

	Cancer prevention	Cancer survivorship
Physical activity	Adopt a physically active lifestyle Engage in at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity activity each week Limit sedentary behavior, such as sitting down, watching television, or other forms of screen-based entertainment	Adopt a physically active lifestyle Engage in at least 150 minutes of physical activity each week Do strength training exercises at least 2 days each week Avoid inactivity Return to normal activities as soon as possible following diagnosis
Weight management	Achieve and maintain a healthy weight throughout life Be as lean as possible without being underweight Avoid excess weight gain at all ages	Achieve and maintain a healthy weight Limit consumption of high calorie foods and beverages Increase physical activity to promote weight loss if overweight or obese
Diet	Consume a healthy diet, with an emphasis on plant foods Limit consumption of processed meat or red meat Eat at least 2.5 cups of vegetables and fruits each day Choose whole grains over refined grain products Limit alcohol consumption to 1 drink or less per day (for women)	Consume a healthy diet Achieve a diet pattern that is high in vegetables, fruits, and whole grains Follow the American Cancer Society guidelines for diet for cancer prevention

in EC, one of the most adipose-sensitive malignancies. Obesity also impacts EC survivorship, as survivors face great morbidity and mortality from obesity-related cardiovascular disease,<sup>7</sup> and obese survivors have much higher cancer-specific mortality rates.<sup>8</sup> Simultaneously, the incidence of ovarian cancer (OC), the deadliest of gynecologic malignancies, may increase as the baby boomer population ages and life expectancy increases.<sup>9</sup> Understanding the opportunities to prevent cancer and optimize the quality of life (QoL) for survivors is critical.

Moreover, for those diagnosed with nongynecologic cancers, research shows that lifestyle and pharmacologic interventions reduce cancer incidence. For example, maintenance of a healthy weight and adhering to a Mediterranean diet reduces the risk of breast cancer,<sup>10</sup> and taking aspirin daily reduces the risk of colon cancer.<sup>11</sup> Table 1 provides the American Cancer Society (ACS) recommendations for weight, diet, and physical activity related to cancer prevention and survivorship.<sup>12,13</sup>

In this review, we synthesize recent advances in understanding the role of modifiable lifestyle factors, such as obesity, in the prevention and management of EC and OC. We highlight the opportunities for lifestyle intervention in both primary prevention and cancer survivorship, including exciting new advances in chemoprevention and prophylactic surgery.

## Opportunities for prevention of EC Background

In the US alone, there were an estimated 50,000 new cases of EC and >10,000 EC-related deaths in 2015.<sup>14</sup> Obesity

and sedentary behavior significantly contribute to risk of EC, specifically for type 1 (estrogen dependent) EC.<sup>15</sup> In obese persons, excess adipocytes convert androgens to estradiol, which stimulates endometrial proliferation, leading to hyperplasia and ultimately cancer.<sup>16</sup> Insulin resistance and diabetes, also highly associated with obesity, have independently been implicated in EC pathogenesis and are additional risk factors.<sup>17</sup>

## Lifestyle prevention

### Obesity and physical activity

Approximately 50% of all new diagnoses of EC are attributable to obesity alone.<sup>18</sup> Obese women have 2.4–4.5 times the risk of being diagnosed with EC compared with normal-weight women with a dose–response relationship between obesity and EC risk.<sup>19–21</sup> Even after adjustment for other risk factors (eg, smoking, oral contraceptive pill [OCP] use, hormone replacement therapy [HRT] use, and parity), an obese woman with BMI  $\geq 40$  kg/m<sup>2</sup> has seven times the odds of developing type 1 EC compared to a normal-weight woman.<sup>21</sup> Additionally, the obesity epidemic appears to have increased EC diagnoses in younger women: incidence rates in women aged <50 years increased by 2% each year from 1992 to 2012.<sup>22</sup>

There are few studies evaluating intentional weight loss and EC risk. A large prospective cohort study found a small, nonsignificant reduction in risk with intentional weight loss of at least 20 pounds (relative risk [RR] =0.96, 95% confidence interval [CI] 0.61–1.52).<sup>23</sup> More extreme weight loss as a result of bariatric surgery does significantly reduce EC risk (see “Surgical prevention” section).<sup>24</sup> However, this weight loss needs to be sustained, as both weight cycling (losing

and regaining weight repeatedly) and adult weight gain have been associated with increased EC risk.<sup>25,26</sup>

For exercise, two meta-analyses of 20 cohort and case-control studies have demonstrated a 20%–30% reduction in EC risk in women who report moderate or high intensity exercise compared to nonexercisers.<sup>27,28</sup> The Nurses' Health Study, a large prospective cohort study started in 1976, demonstrated a temporal effect of exercise on EC risk: women who reported recent high-intensity exercise had a 35% reduced risk of EC compared to those who did not perform any vigorous activity (RR = 0.65, 95% CI 0.47–0.88). Additionally, daily walking in otherwise sedentary women reduces risk.<sup>29</sup> Another large cohort study, the ACS Prevention Study II Nutrition, found reduced EC risk with physical activity only in overweight or obese women, suggesting that women at the highest risk may glean the most benefit.<sup>30</sup>

## Diet

Several studies have examined the relationship between diet and EC risk. In the dietary modification randomized controlled trial (RCT) of the Women's Health Initiative, postmenopausal women randomized to a low-fat diet rich in fruits, vegetables, and grains showed no difference in EC incidence after an average follow-up of 8 years.<sup>31</sup> Although case-control studies suggest that the Mediterranean diet may be associated with a decreased risk of EC,<sup>32</sup> prospective data from over 84,000 women in the Women's Health Initiative cohort study demonstrated no risk difference.<sup>33</sup> In contrast, diets with high glycemic loads increased EC risk by up to 20% in two large meta-analyses of cohort and case-control studies (RR = 1.2, 95% CI 1.06–1.37<sup>34</sup> and 95% CI 1.09–1.33<sup>35</sup>). A meta-analysis found no effect of dairy on EC risk.<sup>36</sup>

## Coffee, tea, alcohol, and other beverages

Coffee consumption may lower EC risk: a meta-analysis of 13 cohort studies found a dose-response relationship and an overall reduced risk of EC with coffee consumption (RR = 0.80, 95% CI 0.74–0.86 for highest vs lowest coffee drinkers).<sup>37</sup> Similar reductions have been noted with green tea consumption, but not black tea.<sup>38</sup> For alcohol, a meta-analysis of six cohort and 14 case-control studies found no association with EC.<sup>39</sup> Sugar-sweetened beverages, on the other hand, may increase the risk of type 1 EC independent of BMI, as demonstrated in one case-control study (RR = 1.78, 95% CI 1.31–2.40).<sup>40</sup>

## Smoking

Smoking decreases the risk of EC, perhaps through antiestrogenic effects. In a meta-analysis of ten cohort studies, the

risk was reduced by 19% (95% CI 0.74–0.88).<sup>41</sup> However, given many known negative health consequences of smoking, it cannot be recommended for EC prevention.<sup>2</sup>

## Surgical prevention

### Bariatric surgery

A meta-analysis of three cohort studies found a 60% reduction in risk of EC after bariatric surgery compared to obese controls who did not have surgery (RR = 0.4, 95% CI 0.2–0.79).<sup>24</sup> This risk reduction may be as high as 81% in women who are able to achieve and maintain a normal weight after surgery.<sup>42</sup> Additionally, the prevalence of asymptomatic endometrial hyperplasia in obese women presenting for bariatric surgery ranges from 7% to 10%.<sup>43–45</sup> In a small study of four patients with endometrial hyperplasia at the time of bariatric surgery, three had complete resolution 2 years later, likely due to weight loss (average loss 41 kg).<sup>46</sup>

## Chemoprevention

### Oral contraceptives pills

Progestin-containing contraceptives, such as OCPs, have antiestrogenic effects on the endometrium and decrease EC risk. A meta-analysis of 36 case-control studies showed a 31% risk reduction in women who had ever used OCPs compared to never users (RR = 0.69, 99% CI 0.66–0.73).<sup>47</sup> Longer use of OCP resulted in lower EC incidence, and the effects persisted for at least 30 years after cessation of use. Despite reductions in OCPs' estrogen content since the 1960s, the risk reduction was the same, suggesting that the progesterone effect was similar regardless of estrogen dose.<sup>47</sup>

### Other contraceptive types

One large case-control study found that injectable progestin (depot medroxyprogesterone acetate) is similarly protective against EC, with effects lasting up to 8 years (RR = 0.21, 95% CI 0.06–0.79).<sup>48</sup> For levonorgestrel intrauterine devices (IUDs), a pooled analysis of four cohort and 14 case-control studies found a 31% reduction in odds of EC, with stronger effects with longer use (odds ratio [OR] = 0.69, 95% CI 0.58–0.82).<sup>49</sup>

## Hormone replacement therapy

There is strong evidence that estrogen-only HRT increases the risk of EC in women with an intact uterus.<sup>50</sup> However, when combined therapy is used, the addition of continuous progestin mitigates EC risk.<sup>50</sup> Both the Women's Health Initiative RCT<sup>51</sup> and the Million Women Study, a UK cohort study, demonstrated that combined continuous HRT does

**Table 2** Summary of recent meta-analyses on endometrial cancer prevention

	Direction of risk	Relative risk (95% CI)	Studies included
<b>Lifestyle prevention</b>			
Obesity (BMI >30) <sup>20</sup>	↑	2.54 (2.11–3.06)*	7 cohort, 11 case–control
Physical activity <sup>27</sup>	↓	0.77 (0.70–0.85)*	7 cohort
Dairy intake <sup>36</sup>	No effect	0.97 (0.93–1.01) <sup>a</sup>	1 cohort, 8 case–control
Coffee intake <sup>37</sup>	↓	0.8 (0.74–0.86)*	13 cohort
Tea intake <sup>38</sup>	No effect	Green tea: 0.78 (0.66–0.92)* Black tea: 0.99 (0.79–1.23)	Green tea: 1 cohort, 5 case–control Black tea: 5 cohort, 4 case–control
Red meat intake <sup>36</sup>	↑	1.51 (1.19–1.93)*	7 case–control
Alcohol intake <sup>39</sup>	No effect	0.83 (0.59–1.18) (cohort analysis) 0.89 (0.76–1.05) (case–control analysis)	6 cohort, 14 case–control
Smoking <sup>41</sup>	↓	0.81 (0.74–0.88)* (cohort analysis) 0.72 (0.66–0.79)* (case–control analysis)	10 cohort, 24 case–control
Breastfeeding <sup>60</sup>	↓	0.77 (0.62–0.96)	14 cohort
<b>Surgical prevention</b>			
Bariatric surgery <sup>24</sup>	↓	0.4 (0.2–0.79)*	3 cohort
<b>Chemoprevention</b>			
Oral contraceptive pills <sup>47</sup>	↓	0.69 (0.66–0.73) <sup>b,*</sup>	15 cohort, 21 case–control
Levonorgestrel intrauterine device <sup>49</sup>	↓	0.69 (0.58–0.82) <sup>c,*</sup>	4 cohort, 14 case–control
Estrogen-only HRT <sup>50</sup>	↑	2.3 (2.1–2.5)*	10 cohort, 27 case–control
Combined estrogen–progesterone HRT <sup>50</sup>	↓	0.4 (0.2–0.6)*	1 RCT, 3 cohort, 3 case–control
Nonsteroidal anti-inflammatory drugs <sup>53</sup>	↓	Overall: 0.87 (0.79–0.96)* Obese: 0.72 (0.58–0.90)* Nonobese: 1.08 (0.82–1.43)	4 cohort, 5 case–control

**Notes:** \*Significant at  $P < 0.05$ . <sup>a</sup>Odds ratio shown, per serving of dairy per day. <sup>b</sup>99% CI given. <sup>c</sup>Odds ratio shown.

**Abbreviations:** CI, confidence interval; BMI, body mass index; RCT, randomized controlled trial; HRT, hormone replacement therapy.

not increase EC risk. In fact, in the Million Women Study, it actually lowered the risk (RR = 0.71, 95% CI 0.56–0.90), whereas regimens with cyclic progesterone or unopposed estrogen increased EC risk.<sup>52</sup>

### Other chemopreventive strategies

Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease EC risk. A meta-analysis of nine case–control studies found a reduction in risk in obese women only (RR = 0.72, 95% CI 0.58–0.90).<sup>53</sup> These data are encouraging, but there is a lack of randomized or prospective data to support NSAID use to reduce EC risk.

Metformin has antiproliferative effects on hyperplastic and cancerous endometrium *in vitro*.<sup>54,55</sup> However, the three large cohort studies are conflicting and inconclusive on the clinical benefits of metformin for EC prevention.<sup>56–58</sup> One trial is currently recruiting obese postmenopausal women at high risk for EC to see whether metformin in combination with lifestyle changes could decrease EC occurrence.<sup>59</sup>

### Breastfeeding

A recent meta-analysis found that breastfeeding reduces the risk of EC by 33% (RR 0.77, 95% CI 0.62–0.96). They also demonstrated a dose–response relationship: for each 1 month

of breastfeeding duration, risk of EC was reduced by 2% (RR 0.98, 95% CI 0.97–0.99).<sup>60</sup>

## Summary and recommendations

Women at risk for EC should be counseled on the benefits of increasing physical activity, even light or moderate activity, as well as the benefits of weight loss for EC risk reduction. Morbidly obese women (BMI  $\geq 40$  kg/m<sup>2</sup>) should be counseled about the health benefits of bariatric surgery, including the impressive EC risk reduction. While no particular diet appears to reduce EC risk, sugar-sweetened beverages and diets with high glycemic load should be avoided. Women should also be counseled about the benefits of EC risk reduction with progestin-containing contraceptives. Table 2 summarizes the findings of included meta-analyses.

## Opportunities for improved management and survivorship in EC Background

There are an estimated 610,000 women with a history of EC in US alone.<sup>61</sup> Most EC patients present early with symptoms, so the majority are cured surgically with or without adjuvant therapy. The RR of mortality is 6.25 times higher in morbidly obese survivors compared to normal-weight survivors.<sup>8</sup>

In fact, EC survivors are more likely to die of cardiovascular disease than cancer.<sup>7</sup> As such, addressing risk factors for cardiovascular disease at the time of EC diagnosis could have the greatest impact on survival.<sup>7</sup>

### Obesity and physical activity

A Cochrane analysis of 56 RCTs of exercise during cancer treatment, including EC treatment, demonstrated a significant improvement in health-related QoL with exercise ranging from yoga to strength training.<sup>62</sup> Obese EC survivors stand to gain from positive effects of exercise, as surveys indicate that they have lower QoL than normal-weight survivors.<sup>63</sup> Nonetheless, most EC survivors are not able to meet the physical activity guidelines. Only 1% of early-stage EC survivors are able to meet all the ACS guidelines (Table 1), and only 12% are able to meet the physical activity guidelines, which has been associated with worse QoL and fatigue.<sup>64</sup>

EC survivors frequently report wanting to eat better, be healthier, and lose weight.<sup>65,66</sup> Yet only 50% of women with history of endometrial hyperplasia or cancer survivors are aware that obesity contributed to their cancer risk.<sup>67</sup> Gynecologic oncologists are not trained to discuss obesity management,<sup>68</sup> and only 10% members of the Society for Gynecologic Oncology reported having any training in weight loss counseling; however, those formally trained were more comfortable discussing weight loss with patients.<sup>68</sup> EC survivors report finding weight loss counseling motivating and denied that it undermined the physician–patient relationship, preferring that their oncologist give specific recommendations for lifestyle improvement.<sup>69</sup>

Several recent studies conducted lifestyle interventions as shown in Table 3.<sup>70–73</sup> The survivors of uterine cancer empowered by exercise and healthy diet (SUCCEED) RCT showed significant weight loss, increased physical activity, greater fruit and vegetable consumption, and improved QoL in EC survivors after an intensive 6-month group and individual lifestyle intervention.<sup>70,71</sup> The Steps to Health study found similar results with a home-based exercise intervention with significant improvement in physical activity, heart rate, and systolic blood pressure in obese and nonobese participants.<sup>73</sup> Low-cost intervention with a mobile health application *Loseit!* also showed short-term weight loss in EC survivors. The revving-up exercise for sustained weight loss by altering neurological reward and drive (REWARD) RCT is currently recruiting obese EC survivors to study different types of exercise and weight loss.<sup>74</sup>

However, not all exercise studies have been successful: Rossi et al<sup>66</sup> recruited ethnically diverse, low-income women

with a history of EC. While 86% of the women surveyed expressed some interest in joining a free exercise program, only 5% came to the scheduled exercise classes. The authors emphasize the fact that care needs to be taken to determine barriers to exercise in vulnerable low-income and/or minority populations.

### Diet

Few studies differentiate the effect of diet alone and its effect on EC survivorship. EC survivors who report meeting the ACS recommendations for diet, physical activity, and abstaining from smoking have higher QoL.<sup>75</sup> In the absence of EC-specific dietary interventional trials, EC survivors should be counseled on the ACS recommendations for healthy eating, given their other benefits.

### Medications

Metformin has been evaluated in EC survivors with conflicting results. Although a large retrospective cohort study reported that women with diabetes on metformin at the time of EC diagnosis had improved recurrence-free survival and overall survival, two subsequent cohort studies failed to replicate this benefit.<sup>76–78</sup> A recent retrospective cohort study suggested that there may be lower recurrence rates in metformin users, but only in those with type 1 EC.<sup>79</sup> Given the need for prospective data, there are multiple metformin trials ongoing, including one evaluating the addition of metformin to standard platinum-based chemotherapy for patients with advanced stage or recurrent EC.<sup>80</sup>

## Summary and recommendations

EC survivors are frequently overweight and inactive. Several RCTs have demonstrated that physical activity and dietary counseling interventions improve weight loss and QoL, although the studies were small and heterogeneous. All providers caring for EC survivors, especially gynecologic oncologists, need more and better training to discuss lifestyle interventions at the time of diagnosis. While diet does not appear to affect EC survivorship, metformin shows promise as an agent to reduce recurrence risk.

## Opportunities for prevention of OC Background

In 2015, there were an estimated 21,000 cases of OC and over 14,000 deaths in the US.<sup>14</sup> The incidence of epithelial ovarian cancer (EOC), which makes up over 90% of OC, is predicted to increase as the world's population ages.<sup>9</sup> As EOC remains the deadliest gynecologic cancer, much of the recent research focuses on prevention.

**Table 3** Lifestyle interventions in survivors of endometrial cancer

	Study design		Intervention		Results		Quality of life
					Adherence, %	Weight change, physical activity, diet	
<b>Completed studies</b>							
Survivors of Uterine Cancer Empowered by Exercise and Healthy Diet (SUCCEED trial) von Gruenigen et al <sup>70</sup> McCarrroll et al <sup>71</sup>	RCT N=75 Overweight or obese stage I or II EC survivors Diagnosed in the past 3 years with no active disease Setting: US clinic	Intervention: education and counseling with 10 weekly and 6 bi-weekly sessions followed by 6 additional months of contact with registered dietician Comparison: usual care Duration: 6 months Follow-up: 6 months	84	Weight change (difference between intervention and comparison): 4.6 kg loss (P<0.001) Physical activity: 100 min/wk increase (6 months, P=0.04), 89 min/wk increase (12 months, P=0.02)	Physical functioning: significant improvement at 6 months (P=0.05) Fatigue: significant improvement at 3 months (P=0.01) Weight loss self-efficacy: significant improvement at 12 months (P<0.001) Fatigue: significant improvement post-intervention (P=0.05) and at 3-month follow-up (P=0.01) Physical functioning: NS		
Donnelly et al <sup>56</sup>	RCT N=33 Stage I–III sedentary ovarian (N=12) and EC survivors (N=11) ≤3 years post-diagnosis Setting: Irish clinic Uncontrolled pre–post	Intervention: behavior change, moderate intensity physical activity Comparison: usual care Duration: 12 weeks Follow-up: 3 months	88	Body composition: NS Physical activity: NS	QoL: NS Weight loss self-efficacy: significant improvement (P=0.04)		
Loseit! App intervention McCarrroll et al <sup>72</sup>	N=50 Overweight or obese stage I or II breast and EC survivors Diagnosed in the prior 3 years with no active disease Setting: US clinic Uncontrolled pre–post	Intervention: three in-person counseling visits, diet, lifestyle, and exercise counseling through the Loseit! App. Participants logged daily weight, food choices, and exercise and received real-time feedback through app Duration: 4 weeks Follow-up: immediately post-intervention	70	Weight change: 2.3 kg loss (P<0.001) Physical activity: 182 min/wk increase (P=0.001)			
Steps to Health Basen-Engquist et al <sup>73</sup>	N=100 Stage I–III A EC survivors At least 6 months post-treatment with no evidence of disease and not meeting exercise guidelines Setting: US clinic	Intervention: individualized exercise plan developed from initial laboratory assessment, home-based exercise with daily exercise diary and accelerometer, telephone counseling at weekly to monthly intervals Comparison: none Duration: 6 months Follow-up: immediately post-intervention	NR	Physical activity: 9 min/d increase (P=0.002) Resting heart rate: significant decrease (P=0.047) Systolic blood pressure: significant decrease (P=0.03) VO <sub>2</sub> max (aerobic capacity): NS Improvements seen in obese and nonobese survivors	Physical functioning: significant improvement (P<0.001) General health: significant improvement (P<0.001) Mental health: significant improvement (P=0.03)		

**Upcoming trials**

**Rewinding Exercise for Sustained Weight Loss by Altering Neurologic Reward and Drive (REWARD trial)**  
Nock et al<sup>74</sup>

**RCT**  
Anticipated accrual: 120  
Obese stage I EC survivors  
Treatment completed > 8 weeks and < 4 years ago  
Setting: US clinic

Intervention: "assisted" rate exercise, 3x/wk – mechanical assistance to adjust participants' heart rate to a goal  
Comparison: exercise intervention at "voluntary rate" 3x/wk  
Both groups receive a dietary behavioral program  
Duration: 16 weeks  
Follow-up: 24 weeks

Currently recruiting patients  
Outcomes: weight change, fitness, body fat, exercise motivation, eating and appetitive behavior measures, QoL, and brain fMRI responses to food

**Abbreviations:** RCT, randomized controlled trial; EC, endometrial cancer; NS, nonsignificant; QoL, quality of life; NR, not reported; fMRI, functional magnetic resonance imaging; wk, week; App, application.

**Lifestyle prevention****Weight loss and physical activity**

Obesity may be a risk factor for OC, although its effect is much less than for EC. While the Women's Health Initiative cohort and Nurses' Health Study found no association, a meta-analysis of 47 studies reported a 12% increased risk of EOC for obese women (BMI >30 kg/m<sup>2</sup>) (99% CI 1.05–1.19, adjusted for age, parity, hysterectomy, menopausal status, OCP usage, HRT usage, and height).<sup>81–83</sup> Physical activity appears to offer a modest preventive benefit: a review of 26 studies found mixed effect in cohort studies but a significant risk reduction among the most active women in case–control studies.<sup>84</sup> A meta-analysis of nine cohort and ten case–control studies reported an 8% nonsignificant risk reduction (95% CI 0.84–1.00) for any physical activity versus no physical activity and a nonsignificant 11% risk reduction (95% CI 0.79–1.01) for high levels of physical activity versus none.<sup>85</sup> The majority of physical activity studies included in these meta-analyses were controlled for age, BMI, and family history of OC.

**Diet**

The sole diet RCT, the Women's Health Initiative trial, found reduction in EOC risk with a low-fat diet with a hazard ratio (HR) of 0.60 (95% CI 0.38–0.96) at 8 years post-intervention but not at 4 years post-intervention, suggesting that long-term adherence to a low-fat diet was needed for benefit.<sup>31</sup> Cohort studies, including the Nurses' Health Study, have found no significant association between fat intake and EOC incidence.<sup>86,87</sup> The Nurses' Health Study also found no association with two healthy eating indices or a Mediterranean diet.<sup>88,89</sup>

Vegetable intake may have a small impact on EOC risk: two meta-analyses of cohort and case–control studies reported 11%–16% risk reduction with daily vegetable consumption (95% CI 0.81–0.99 and 0.75–0.94, respectively).<sup>90,91</sup> Meta-analyses have found no significant association with dairy,<sup>92</sup> fish,<sup>93</sup> fiber, or dietary and antioxidant nutrients.<sup>87</sup>

**Coffee, tea, alcohol, and other beverages**

Coffee and tea are thought to have antioxidant and anti-inflammatory properties, although the benefit is unproven in EOC. A meta-analysis of seven cohort and case–control studies, including the Nurses' Health Study, found no association between coffee and EOC incidence.<sup>94</sup> One case–control study published later reported a modest decrease in odds with increasing coffee consumption (OR =0.90, 95% CI 0.84–0.97 per cup/d) and total caffeine consumption (OR =0.93, 95% CI 0.88–0.98 per 100 mg/d), significant only for serous tumors.<sup>95</sup>

For tea, a systematic review of 16 studies and a meta-analysis of six case-control studies found no association.<sup>94,96</sup> The Nurses' Health Study has since reported decreased odds with one or more cups of black tea per day (OR =0.68, 95% CI 0.51–0.90).<sup>97</sup> For green tea, a meta-analysis of six case-control studies reported decreased odds with consumption of one or more cups per day (OR =0.81, 95% CI 0.73–0.89).<sup>98</sup>

Sugar-sweetened beverages appear to have little to no effect on EOC incidence in two cohort and one case-control studies.<sup>99–101</sup>

While alcohol increases the risk of breast and other cancers, there appears to be no association with EOC. Three meta-analyses of cohort and case-control studies found no overall association with heavy, moderate, or low levels of drinking overall with a possible protective effect on endometrioid EOC only (RR =0.82, 95% CI 0.70–0.96).<sup>102–104</sup>

## Smoking

While most types of EOC are not associated with smoking, a meta-analysis of 51 studies found an increased risk of mucinous EOC (RR =1.79, 95% CI 1.60–2.00), with a dose-response relationship for pack-years of smoking.<sup>105–107</sup> Smoking cessation should be recommended for all women.

## Breastfeeding

A meta-analysis of five cohort and 35 case-control studies reported a 24% reduction in EOC risk (95% CI 0.69–0.83), and longer duration of breastfeeding was associated with decreased odds of EOC.<sup>108,109</sup>

## Surgical prevention

### Tubal ligation and salpingectomy

It is now believed that the majority of EOCs arise from abnormalities in the fallopian tube. Tubal ligation decreased the risk of EOC by up to 30% in the most recent meta-analysis of seven cohort and 23 case-control studies (95% CI 0.64–0.75).<sup>110</sup> The Society for Gynecologic Oncology recommends salpingectomy after childbearing is complete during elective pelvic surgeries, hysterectomy, or as an alternative to tubal ligation.<sup>111</sup> Bilateral salpingo-oophorectomy for those at high genetic risk (eg, *BRCA1* and two mutation carriers) is recommended at age 35 or upon the completion of childbearing and decreases their risk of OC by 80%.<sup>112</sup>

## Chemoprevention

### Oral contraceptive pills

A meta-analysis of 13 cohort and 32 case-control studies found a 27% risk reduction in EOC in ever versus never users

(95% CI 0.70–0.76) with a dose-response relationship and persistent benefits up to 30 years after use. Similar risk reductions were seen for epithelial and nonepithelial tumors, but OCPs appeared to have little effect on mucinous tumors.<sup>113</sup> Low-dose estrogen OCPs, the most commonly used at present, may provide the greatest risk reduction.<sup>114</sup>

### Other contraception types

There is no conclusive evidence that non-OCP contraception prevents EOC. For injectable progestin contraception, two case-control studies found reductions in odds of EOC of 39% (95% CI 0.44–0.85) for any use and 93% for 5 years of use (95% CI 0.01–0.49),<sup>115,116</sup> while prior case-control<sup>117</sup> and cohort<sup>118</sup> studies found no significant association. For IUDs, no association was found in one cohort study and two case-control studies. These studies were conducted in the People's Republic of China where nonhormonal IUDs (steel ring) are the most common.<sup>119–121</sup>

### Hormone replacement therapy

The 2002 Women's Health Initiative trial showed an increased risk of cardiovascular disease, breast cancer, and possibly EOC with HRT.<sup>122,123</sup> A meta-analysis of 17 cohort and 38 case-control studies found a 37% increased risk of EOC (95% CI 1.27–1.48) for ever users of HRT compared to never users, consistent with the possible risk increase in the Women's Health Initiative RCT.<sup>124</sup> There were similar risks with estrogen-only and estrogen-progesterone formulations, and risk was significantly increased with serous and endometrioid cancers. While risks decreased in ex-HRT users, the increased risk persisted for 5 years after stopping HRT.<sup>125</sup> However, the absolute risk is low with an estimated increase of one extra case among 1,000 HRT users and one extra death from EOC among 1,700 HRT users.

### Other chemopreventive strategies

Both statins and NSAIDs have been proposed for chemoprevention, given their anti-inflammatory properties. For statins, one case-control study found no association with EOC risk, but research is ongoing.<sup>126,127</sup> For NSAIDs, no association or dose-response relationship was seen in the one RCT or the Nurses' Health Study cohort, and four recent meta-analyses suggest limited to no benefit.<sup>128–133</sup> However, aspirin specifically is associated with a modest reduction in risk (OR 0.91, 95% CI 0.84–0.99) and research is ongoing.<sup>130</sup> NSAIDs are not currently recommended for EOC prevention in the absence of another indication for use.



**Table 4** Summary of recent meta-analyses on ovarian cancer prevention

	Direction of risk	Relative risk (95% CI)	Studies included
<b>Lifestyle prevention</b>			
Obesity (BMI >30) <sup>81</sup>	↑	1.13 (1.06–1.20) <sup>a,*</sup>	17 cohort, 30 case–control
Physical activity <sup>84</sup>	No effect	0.92 (0.84–1.00)	9 cohort, 10 case–control
Vegetable intake <sup>89,90</sup>	↓	0.89 (0.81–0.99) <sup>*</sup>	4 cohort, 4 case–control
Dairy intake <sup>91</sup>	No effect	0.925 (0.78–1.09) <sup>b</sup>	19 case–control
Fish intake <sup>92</sup>	No effect	1.04 (0.89–1.22) (cohort analysis) 0.90 (0.73–1.12) (case–control analysis)	5 cohort, 10 case–control
Coffee intake <sup>93</sup>	No effect	1.05 (0.75–1.46)	7 case–control
Tea intake <sup>93,95</sup>	No effect	1.07 (0.78–1.45)	6 case–control
Alcohol intake <sup>101</sup>	No effect	1.03 (0.96–1.10)	13 cohort
Smoking <sup>105</sup>	↑	1.07 (1.03–1.10) <sup>a,*</sup>	19 cohort, 21 case–control
Breastfeeding <sup>107</sup>	↓	0.76 (0.69–0.83) <sup>*</sup>	5 cohort, 35 case–control
<b>Surgical prevention</b>			
Tubal ligation <sup>109</sup>	↓	0.7 (0.64–0.75) <sup>*</sup>	7 cohort, 23 case–control
<b>Chemoprevention</b>			
Oral contraceptive pills <sup>112</sup>	↓	0.73 (0.70–0.76) <sup>*</sup>	13 cohort, 32 case–control
Hormone replacement therapy (estrogen only and combined) <sup>123</sup>	↑	1.14 (1.10–1.19) <sup>*</sup>	17 cohort, 35 case–control
Nonsteroidal anti-inflammatory drugs <sup>129</sup>	No effect	Aspirin: 0.91 (0.84–0.99) NSAIDs: 0.90 (0.77–1.05) Acetaminophen: 0.99 (0.88–1.12)	12 case–control

**Notes:** <sup>a</sup>Significant at  $P < 0.05$ . <sup>a</sup>99% CI given. <sup>b</sup>Odds ratio shown is for 13 studies of low-fat/skimmed milk as dairy studies were analyzed by main type of dairy.

**Abbreviations:** CI, confidence interval; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug.

Similar to EC, metformin is thought to inhibit cellular pathways involved in some EOCs. One cohort<sup>56</sup> and one case–control study<sup>134</sup> found a nonsignificant trend toward reduced risk of EOC with use, while two other cohorts found no association between EOC and metformin use.<sup>58,135</sup>

Table 4 summarizes findings of included meta-analyses.

## Summary and recommendations

While physical activity and diet do not majorly affect EOC risk, women should be counseled on the benefits of maintaining a healthy weight and active lifestyle for overall health. Obese women should be counseled on the modest increased risk of EOC, and smoking should be strongly discouraged. Women considering different contraceptive options should be counseled on preventive benefits of OCPs and tubal ligation or salpingectomy for EOC risk reduction.

## Opportunities for improved management and survivorship in OC Background

OC continues to have a high mortality rate with median survival of 40%–50% at 10 years. Many patients who initially respond to chemotherapy and surgery have EOC recurrence, which is often incurable.<sup>9</sup> In this context, QoL is important,

and lifestyle interventions may play a role in optimizing survivors' experiences.

### Obesity and physical activity

Obesity may affect survival and QoL after EOC diagnosis. A meta-analysis of 21 case–control studies reported increased mortality risk of 1.12 (95% CI 1.01–1.25) for women with BMI  $\geq 35.0$  kg/m<sup>2</sup> as well as negative effects of obesity on progression-free survival and EOC-specific survival.<sup>136</sup> In contrast, the Women's Health Initiative cohort found no association of BMI and mortality after EOC diagnosis.<sup>83</sup> QoL may be lower in obese survivors, but further research is needed.<sup>137</sup>

Surveys suggest that most EOC survivors are inactive, with only 19% meeting ACS guidelines.<sup>138,139</sup> Yet similar to EC, in two cross-sectional studies, exercise has been associated with improved QoL and mental health and reduced fatigue in EOC survivors.<sup>140,141</sup> The Women's Health Initiative cohort study reported that vigorous physical activity prior to diagnosis was associated with a 24% lower risk of overall mortality (95% CI 0.58–0.98) compared with no vigorous physical activity.<sup>83</sup> However, fatigue may be one of the biggest barriers to exercise during or post-treatment, especially in women without established exercise routines.<sup>139,142</sup>

Table 5 presents the five small studies examining the impact of exercise interventions on EOC survivors.<sup>140,143–146</sup>

Table 5 Lifestyle interventions in survivors of OC

	Intervention		Results		
	Study design	Intervention	Adherence, %	Weight change, physical activity, diet	Quality of life
<b>Completed studies</b>					
Ovarian Nutrition Education (ONE) study Paxton et al <sup>147</sup>	RCT N=51 Stage II-IV OC survivors Setting: US clinic	Intervention: weekly to monthly telephone calls with dietitian advising diet with $\geq 5$ vegetable servings/d, 16 ounces of vegetable juice/d, $\geq 3$ fruit servings/d, $\geq 30$ grams of fiber, and $\leq 20\%$ energy from fat Comparison: weekly to monthly telephone calls with dietitian advising diet with $\geq 5$ fruit and/or vegetable servings/d, $\geq 25$ grams of fiber, $\leq 20\%$ energy from fat, four fruit and vegetable capsules, and a soy-based beverage supplementation Duration: 6 months Follow-up: immediately post-intervention	11–33	Weight: NS Serum albumin: NS CA-125: NS Dietary, significant increase in juice, intake ( $P=0.02$ ), NS for energy, vegetable, fat, or fiber intake	QoL: NS Fatigue: NS Pain: NS
Moonsammy et al <sup>144</sup>	Controlled pre–post N=19 women Intervention: seven newly diagnosed epithelial ovarian, fallopian, or primary peritoneal cancer Comparison: 12 women previously treated for ovarian, fallopian tube, or peritoneal cancer Setting: Canadian clinics	Intervention: individualized home-based exercise program and equipment (stability ball, yoga mat, resistance bands), biweekly telephone-based cognitive behavior therapy Comparison: surveillance, biweekly telephone-based cognitive behavior therapy Duration: 24 weeks Follow-up: immediately post-intervention	NR	Body composition: significant increase in body fat ( $P=0.03$ ) and waist circumference ( $P=0.02$ ) $VO_2$ max (aerobic capacity): significant improvement ( $P=0.008$ ) HR: NS	QoL: NS Anxiety: NS
Hwang et al <sup>143</sup>	Controlled pre–post N=40 OC survivors s/p hysterectomy, oophorectomy, and chemotherapy In remission for 0.5–3 years Setting: Korean hospital	Intervention: 1-hour weekly health education and support group, home exercise (three 60-min sessions/wk), relaxation therapy (three 15-min sessions/wk) for 8 weeks Comparison: usual care Follow-up: immediately post-intervention	92	Blood pressure: NS Distance walked: significant improvement ( $P=0.005$ ) Muscle strength: significant improvement ( $P=0.001$ )	QoL: significant improvement ( $P=0.004$ )
von Gruenigen et al <sup>145</sup>	Uncontrolled pre–post N=27 Ovarian, fallopian tube, or peritoneal cancer patients Receiving at least six cycles of adjuvant chemotherapy Setting: US clinic	Intervention: 30-minute dietary and exercise counseling at each chemotherapy session, pedometer Comparison: none Duration: six chemotherapy cycles Follow-up: immediately post-intervention	92	Physical activity: NS Fruit and vegetable intake: NS	QoL: significant improvement ( $P=0.001$ ) Fatigue: NS
Newton et al <sup>146</sup>	Uncontrolled pre–post N=17 Newly diagnosed OC In chemotherapy	Intervention: educational booklet, individualized weekly walking prescription, weekly counseling with exercise physiologist (in-person or by phone, depending on participant distance from hospital) Comparison: none	76	Physical functioning (measured with a 6-minute walk test): significant improvement ( $P=0.01$ )	Physical well-being: significant improvement ( $P=0.01$ ), NS for other QoL measures Symptoms: NS

<p>Mizrahi et al.<sup>39</sup></p>	<p>Setting: Australian hospital</p> <p>Uncontrolled pre-post N=30</p> <p>Recurrent OC</p> <p>On second or third line chemotherapy</p> <p>Setting: Australian clinic</p>	<p>Duration: 11–21 weeks (length of active chemotherapy)</p> <p>Follow-up: immediately post-intervention</p> <p>Intervention: individualized 90 min/wk prescribed exercise, weekly telephone call</p> <p>Comparison: none</p> <p>Duration: 12 weeks</p> <p>Follow-up: 12 weeks</p>	<p>81</p> <p>BMI: NS</p> <p>Heart rate: NS</p> <p>Blood pressure: NS</p> <p>Physical activity: significant improvement (8.8 METs × hour per week, P=0.003)</p> <p>Physical fitness: significant improvement in upper and lower body strength and balance (P=0.002)</p> <p>VO<sub>2</sub> max (aerobic capacity): NS</p> <p>QoL: significant improvement (P=0.001)</p> <p>Fatigue: NS</p> <p>Symptoms: significant improvement in sleep (P=0.04) and mental function (P=0.001)</p> <p>Anxiety, depression: NS</p>
<p><b>Upcoming RCTs</b></p>	<p>1,070 women</p> <p>Stage II, III, or IV of epithelial OC, fallopian tube, or primary peritoneal carcinoma at diagnosis</p> <p>Completed treatment within past 6 weeks to 6.5 months</p> <p>No clinical evidence of persistent or recurrent disease</p>	<p>Intervention: in-person diet counseling, telephone counseling (twice a week to bimonthly), exercise diaries</p> <p>Comparison: telephone check-ins</p> <p>Duration: 12 months</p> <p>Follow-up: 5 years</p>	<p>Currently recruiting patients</p> <p>Outcomes: weight, exercise adherence, and QoL</p>

**Abbreviations:** RCT, randomized controlled trial; OC, ovarian cancer; NS, nonsignificant; QoL, quality of life; NR, not reported; HR, hazard ratio; BMI, body mass index; MET, metabolic equivalent of task; wk, week.

Four studies reported increased physical activity at the end of counseling. Of the two studies on weight change, one reported no significant change and one reported weight gain.<sup>144,147</sup> Three of five studies on QoL reported improvement.<sup>140,144–146</sup> As exercise has significant, noncancer benefits, exercise counseling or other methods to support physical activity should be incorporated into EOC survivorship management.

### Diet

Dietary intervention in EOC survivors is an active area of ongoing research. The Women's Health Initiative cohort found higher quality diet to be associated with lower all-cause mortality, independent of physical activity (HR =0.73, 95% CI 0.55–0.97).<sup>148</sup> As shown in Table 5, one of two interventions showed slight improvements in diet with in-person counseling, and there is one ongoing trial of dietary counseling and exercise in EOC survivors.<sup>145,147,149</sup>

### Medications

Statins have been proposed for prevention of EOC recurrence, and one case-control study found decreased mortality (age-adjusted HR =0.47, 95% CI 0.26–0.85), although further research is needed.<sup>126</sup> Given the link between HRT and EOC incidence, its use in survivors has been recently studied. One meta-analysis of two RCTs and four cohort studies found no increased risk of recurrence with postoperative HRT use.<sup>150</sup> A recent RCT actually reported improved overall and relapse-free survival in women using HRT after surgical or chemotherapy treatment (HR =0.63, 95% CI 0.44–0.90 and HR =0.67, 95% CI 0.47–0.97, respectively).<sup>151</sup>

## Summary and recommendations

Similar to EC, EOC survivors are frequently inactive, and obesity may adversely impact survival and QoL. Small intervention studies show that exercise improves QoL, but the long-term effects on weight and mortality are unknown. Diet does not affect EOC survivorship. HRT appears to be safe in EOC survivors.

## Discussion

The obesity epidemic is driving an alarming increase in lifestyle-related cancers in the US and worldwide.<sup>2,5</sup> As this review shows, modifiable lifestyle factors substantially impact the incidence of EC and OC and the health of cancer survivors. There are multiple areas in which interventions could prevent cancer and improve survivors' QoL.

Obesity increases the risk of EC, increases the risk of OC to a lesser extent, and adversely impacts the health of survivors. Bariatric surgery offers a unique opportunity to prevent EC and reduce other obesity-related morbidities that are the main cause of death for EC survivors. Modeling analyses suggest that bariatric surgery could be cost-effective as part of early-stage EC treatment and would decrease mortality in these patients.<sup>152</sup> Less drastic interventions, such as physician counseling and exercise programs, may also impact EC survival, given promising effects on weight loss from the current small trials, but these interventions are underutilized. Training all women's health providers, including gynecologic oncologists and generalist gynecologists, in obesity counseling is critical to help more women understand and begin to address lifestyle-related cancer risk. However, counseling should be combined with additional interventions to effect meaningful change. A multidisciplinary, collective approach to obese, sedentary at-risk women and survivors of cancer, including collaborations with bariatric surgeons, physical activity counselors, and nutritionists, may help women lose weight and improve their long-term health. Longer term follow-up is also needed to determine whether weight loss impacts cancer recurrence and mortality in survivors. Although the magnitude of obesity's adverse effects is far less with OC, EOC incidence is estimated to increase 3% per decade with current obesity trends.<sup>82</sup> Reducing obesity could reduce the burden of EC and OC as well as many other diseases.

Physical activity has only modest effects on EC prevention, but it improved health and QoL in EC and EOC survivors. For EC, exercise may also be a means to weight reduction, as seen in the few small, heterogeneous studies. For EOC, QoL improvements are particularly meaningful, given the limited life span of most survivors. Exercise should be integrated into gynecologic cancer survivorship care.

Diet and alcohol minimally impact the risk of EC and OC. Eating more vegetables and less red meat may be beneficial, and these recommendations are in line with general guidelines for healthy eating. Smoking increases mucinous EOC risk. Women's health providers should continue to encourage smoking cessation at every available opportunity.

New chemoprevention strategies are on the horizon, such as NSAIDs and metformin, with several current trials ongoing. Several other medications are being studied as well, such as beta-blockers for EOC survivors.<sup>153</sup> HRT, on the other hand, is now firmly established to increase cancer risk for EOC and EC (except combined continuous HRT).

In contrast, OCPs are estimated to have prevented 400,000 cases of EC and 200,000 cases of EOC, including 100,000 EOC deaths, in the past 50 years.<sup>47,113</sup> Nonetheless, OCPs are underutilized for EOC prevention. In fact, 25% of women overall, and 40% of the high-risk women who would be the most likely to benefit, falsely believe that OCPs increase EOC risk.<sup>154,155</sup> OCPs should continue to be included in the counseling of high-risk women as recommended by the Society for Gynecologic Oncology and ACS.<sup>111</sup> Research on potential benefits of other hormonal contraceptives is needed, particularly as more women in developed countries transition to long-acting reversible contraception, such as injectable contraception and IUDs. Finally, as prophylactic tubal ligation and/or salpingectomy enters mainstream practice, continued research will be necessary to evaluate the impact on all-cause and EOC-specific mortality.

We found a paucity of intervention studies on modifiable lifestyle factors in EC and EOC survivors. While this reflects, in part, the newness of these discoveries, even well-established interventions have not been scaled out to reach all those who might benefit. We eagerly anticipate the results of ongoing lifestyle and chemoprevention trials and encourage more researchers to pursue this area from which so many women may benefit.

## Conclusion

Lifestyle factors, such as overweight/obesity and sedentary living, increase the risk of developing EC and OC. As low- and middle-income countries undergo transition to a Western sedentary lifestyle and are further burdened by obesity, addressing modifiable risk factors will be even more important to minimize the gynecologic cancer burden and optimize survivorship globally.

## Disclosure

The authors report no conflicts of interest in this work.

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