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# LIFESTYLE ADVICE TO REDUCE OVARIAN CANCER RISK

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**Abstract – *Objective:*** *Ovarian cancer is usually diagnosed at advanced stages; it has one of the worst prognoses among gynecologic neoplasms and it hasn't got an effective screening program. It has modifiable risk factors in common with endometrial and breast cancer.*

***Materials and Methods:*** *Review of literature in Medline..*

***Results:*** *Risk reduction strategies include body weight normalization, regular exercise, healthy diet largely based on fiber-rich vegetables with antioxidant and anti-inflammatory properties and low glycemic loads, appropriate dose of Vitamin D and strategies to reduce exposure to environmental pollution.*

***Conclusions:*** *Gynecologic consultation is a good opportunity to give advice and improve lifestyle targeted to reduce not only ovarian but also endometrial and breast cancer risk and to promote overall health.*

**KEYWORDS:** *Ovarian neoplasms, Primary prevention, Lifestyle, Diet, Endometrial neoplasms, Breast neoplasms.*

## INTRODUCTION

Ovarian cancer (OC) is the 7th most common neoplasm among women, affecting around 1.5-1.8% women. Approximately one out of 74 women will have OC and one out of 104 will die of this neoplasm[1]. Around 80% of women with OC have high-grade serous carcinoma, and 90% present with stage III or IV disease. OC spreads rapidly, has few initial specific symptoms and 5-year survival remains low at 38-41%[2]. A recent study supports the notion that OC is strongly related to the typical lifestyle of Western or wealthier countries. Authors found a positive and significant ($p<0.05$) correlation between OC incidence and mortality with BMI and measures of country's developmental indicators too[3]. Human Developmental Index (HDI) is a measure of the social and economic status of people in different countries that could be used to assess disparities in cancer incidences and fatality. HDI is a combination of indicators including life expectancy, educational level and income. HDI correlates with BMI and OC outcomes[4]. OC early detection is challenging because of the tubal origin of most high-grade serous OCs, difficulties in differential diagnosis of certain complex adnexal masses at ultrasound, necessity of a laparoscopy to sample ovarian tissue and lack of robust surrogate endpoint biomarkers[5]. Large diagnostic trials have failed to demonstrate the effectiveness of OC screening as it does not reduce mortality and results in false-positive tests with higher rates of oophorectomy and possible complications[6]. To date, the best we can do for an early detection is adding a transvaginal ultrasound at each gynecologic examination. Unfortunately, the rapid tissue growth and the fact that ovarian lesions could already be one of the metastatic sites of primitive

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tubal neoplasms, reduce the sensitivity and specificity of a negative pelvic ultrasound examination. Moreover, ovarian tumor markers have many false positive and false negative results. New markers like HE4 could better help identifying adnexal masses at higher risk of being a cancer[7]. OC is a more frequent neoplasm in wealthier societies, but social and economic status reduction cannot be proposed as a preventative advice for OC primary prevention. Targeting modifiable risk factors such as the main components of a typical Western lifestyle and wealthier societies is much more feasible. Lifestyle and reproductive risk factors such as obesity, reduced childbirth and lactation, age at menarche and menopause, affect ovarian, endometrial and breast cancer risk in parallel. The only exception to common breast and OC risk modulation is estrogen plus progestin hormonal therapy, which appears to slightly increase breast cancer risk while offering some protection against OC[8].

## MATERIALS AND METHODS

Review of literature in Medline following the strategy: ("Ovarian Neoplasms/diet therapy-"[Mesh] OR "Ovarian Neoplasms/prevention and control"[Mesh]) AND "humans"[MeSH Terms]. Out of the 1949 articles the ones inserted in references were selected as pertinent.

## RESULTS

Ovarian cancer is a heterogeneous group of neoplasms deriving from germ cells, stromal or epithelial tissue with different pathogenesis. 5-15% have a genetic origin and are related to a pathogenic mutation in the BRCA or in the MMR genes. Epithelial cancers are the most common type of OC and are classified into high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous carcinomas. Therefore, any lifestyle could hardly reduce any OC subtype risk[9]. As high-grade serous carcinomas have the worst prognosis, the following advices are targeted to reduce their risk and also the risk of most endometrial and breast neoplasms that tend to share common risk factors[10].

Genetic factors, age and adult attained height are important but non-modifiable risk factors. Pregnancy and lactation reduce the risk of OC, and breastfeeding should be proposed to improve infant and maternal health. Hormonal contraception is the most important pharmacological prevention of OC and endometrial cancers, but it could increase breast cancer risk even if the global cancer risk is slightly reduced in users[11]. Therefore, we will focus on risk factors that could be changed by lifestyle adaptations.

### *Normalize weight if overweight or obese*

Being overweight (BMI 25-29 kg/m$^2$) or obese (BMI ≥ 30 kg/m$^2$), is a significant risk factor for OC [12]. About one third of the world's population (35%) is overweight and around 12% are obese [13].

High BMI increases the risk of ovarian and endometrial cancers, postmenopausal breast neoplasms and many other cancers such as colon, rectum, kidney, pancreas and gallbladder.

Endometrial cancer is the neoplasm that is more related to body fatness (HR 1.10, 95% CI 1.09, 1.12 per kg/m$^2$): obese women have a threefold risk of endometrial cancer (HR 3.17, 95% CI 2.52, 3.98). Overweight and obesity combined were estimated to be responsible for 41.9% (95% CI 32.3%, 50.1%) of endometrial cancers in an Australian study that surprisingly didn't find correlation between body fatness and OC [14]. Risk of developing any cancer increases by approximately 3-10% per unit of BMI [15]. BMI is not only a risk factor but also a negative prognostic indicator [16], specifically for epithelial OC and correlates with its clinical and pathological factors [17].

Fatness increases the amount of circulating estrogen that promotes proliferation of ovary surface epithelium and is associated with insulin resistance that causes most of the typical western or wealthier society diseases. Adult attained height seems to be an even more important risk factor than weight, but it is not suitable as a target for lifestyle change. The relative risk for OC per 5 kg/m$^2$ increases in body mass index was 1.1 in women who had never taken menopausal hormone therapy but was only 0.95 in women who had previously taken menopausal hormone therapy [18].

This means that ovarian risk could be reduced by reducing estrogen exposure. Thus, body weight control is the most important advice a gynecologist can give.

### *Increase physical exercise and reduce sedentary*

In women, sitting time is associated with risk of OC (RR=1.43, 95% CI 1.10-1.87) [19]. Sitting time is associated with greater fatality, cardiovascular disease, type 2 diabetes mellitus, obesity and cancer. It is associated with markers of chronic

disease risk such as weight gain, high cholesterol and high fasting insulin levels. Being physically active is the second advice to give after weight control in case of overweight and obese women, and the first in normal weight patients.

### *Eat plenty of vegetables rich in fiber*

Increasing dietary fiber intake through daily diet with cereal, fruit and vegetables is of importance for OC prevention. In a recent meta-analysis, the relative risk of ovarian cancer for the highest *vs.* the lowest category of dietary fiber intake was 0.78 (95% CI: 0.70, 0.88) [20]. An increment of 10 g of fiber a day was associated with a 12% reduction in risk (RR: 0.88; 95% CI: 0.82, 0.93).

In another recent meta-analysis, the relative risk for OC in participants with the highest compared with the lowest fiber intake was 0.760 (95%CI=0.702–0.823) [21]. This association was significant in case-control, cohort studies and in populations from the United States, Europe and Asia in a total of 17 articles with 149,177 participants including 7609 OC patients.

A previous systematic review didn't show such protective effects, but the association is biologically plausible as estrogens are related to the progression of OC stimulating ovarian epithelial cell proliferation and promoting ovarian tumor progression [22, 23]. In a dose-response analysis ovarian cancer risk decreased by 3% (RR, 0.97; 95% CI, 0.95-0.99) for each 5-g/d increment in dietary fiber intake [24].

Dietary fiber may decrease circulating estrogen concentrations by changing gut microbiome, increasing excretion and consequently lowering serum levels and availability of estrogens [25]. Dietary fiber reduces glycemic load and improves insulin sensitivity, decreasing insulin-like growth factor 1 (IGF1) a risk factor for OC development and progression [26].

Diets high in whole grains contain other compounds like phenolic compounds and antioxidants, which may also lower the risk of cancer in general [27].

High dietary fiber intake may also be a marker of 'healthier' lifestyle, such as increased physical activity, that could independently contribute to OC reduction [28]. The mean dietary fiber intake in western countries is about 15 g/day, while the recommended amount is 25–38 g/day. Thus, the advice to increase vegetable consumption is of utmost importance for overall health, not only for OC prevention, as high dietary fiber intake is inversely associated with breast, endometrial, colorectal, gastric, pancreatic and renal cell cancer incidences [29]. Dietary fiber is a protective factor for type 2 diabetes and inflammatory bowel disease too. At the same time, a healthy diet with fiber keeps an adequate abdomen microbiome that helps the immune system to better control gynecologic infections. Gynecologists should advise patients to eat more fruit and vegetables, whole grains, beans and legumes instead of refined flour following the Mediterranean diet indications.

### *Reduce the amount of simple sugars, prefer complex carbohydrates*

Cancer cells depend on aerobic glycolysis for fuel acquisition and, unlike normal cells, are unable to metabolize ketones for energy. The Warburg effect aims at "starving" cancer cells of the glucose and insulin required for proliferation and are a potential adjuvant therapy for OC [30].

Ketogenic diets (KDs) are low-carbohydrate and high-fat diets that shift the fuel source from carbohydrate to fat, reducing blood glucose and insulin while increasing ketone bodies. Preventive benefit for OC is plausible but a recent systematic review highlighted the absence of data regarding the effect of nutritional interventions at least during ovarian oncology treatments [31]. Reducing simple sugars while increasing complex carbohydrates could still be an advice worth giving considering the fundamental importance for gynecologic – obstetric and overall health.

### *Supplement or expose to sunlight if the levels of Vitamin D are low*

Vitamin D deficiency results in an increase in the risk of developing OC, as it plays an important role in cancer prevention by regulating cellular proliferation and metabolism [32].

Adequate Vitamin D food intake, supplements and sunlight exposure may potentially be an efficient way of preventing ovarian neoplasms [33].

Sunlight, specifically ultraviolet-B radiation, is the main pathway for producing adequate levels of Vitamin D. OC incidences and fatality are inversely associated with UVB exposure that is responsible for Vitamin D production in the skin [34]. A population control-based case study found that women who spent their lives in areas with high levels of ambient UV had a lower risk of developing epithelial OC [35]. They reported a greater incidence of OC in North America and northern Europe than in Asia or Africa. Increasing latitude is associated with higher fatality levels [36].

However, a different cohort study found no association between UVB exposure and the risk of OC [37], maybe because there are several Vitamin D Receptor (VDR) genes and other polymorphisms in different individuals or populations that may diversely influence the sun effect on ovarian cells metabolism, apoptosis, inflammation, angiogenesis, metastatic potential and lastly on OC risk.

Overweight and obese women particularly have a Vitamin D deficiency which is associated with an increased risk of OC [38]. Leptin is an adipocyte-derived adipokine that plays a crucial role in regulating appetite and energy balance which is strongly elevated in obese OC patients. The Vitamin D active metabolite 1,25(OH)2D3 has a suppressive effect on leptin induced OC through miR498 pathway. Therefore, 1,25(OH)2D3 and its analogs are promising agents for cancer prevention [39].

A healthy blood level of 25-hydroxy Vitamin D is > 30 ng/mL. Randomized controlled trials using Vitamin D and calcium on post-menopausal women found a more beneficial effect in reducing the incidences of cancer compared with Vitamin D supplement alone, although not all studies agree [40].

As osteoporosis prevention is one of the subjects of discussion in perimenopausal and post-menopausal gynecological consultation, explaining the possible role of Vitamin D in OC prevention could also help patients to be more compliant with Vitamin D prescriptions and sunlight adequate exposures.

### *Prevent pelvic infections, detect them early and treat them adequately*

The fallopian tube lets pro-inflammatory agents ascend from the lower genital tract resulting in inflammation at the tubo-ovarian junction, potentially increasing the risk of genotoxic damage to the ovarian surface epithelium or the formation and closure of inclusion cysts on the ovary. Chronic inflammation can stimulate the release of cytokines and chemokines that contribute to development or activation of malignant diseases [41]. Recurrent pelvic inflammatory disease (PID) is associated with the highest risk of OC OR 1.88 (CI 1.13–3.12) [42]. A history of pelvic inflammatory disease (PID) increases specifically the risk of serous borderline tumors (HR=1.85; 95% CI: 1.52–2.24) but not of mucinous borderline tumors. (HR = 1.06; 95% CI: 0.83–1.35) [43]. Serous borderline tumors originate in the fallopian tube from papillary tubal hyperplasia (PTH) that implants on the ovary: chronic inflammation can induce proliferation of the epithelium and PTH. Mucinous borderline tumors have a different pathogenesis: they develop from benign mucinous tumors originating in paraovarian transitional cell nests.

The role of inflammation on OC explains the protective effect of low-dose aspirin that reduces epithelial OC risk (OR = 0.82; 95% CI 0.68-0.99) with duration effect relation: long-term use (≥ 5 years) of low-dose aspirin (OR = 0.77; 95% CI 0.55-1.08) and continuous long-term use of low-dose aspirin, defined as close consecutive prescriptions, gives further reduction in OR (0.56; 95% CI 0.32-0.97). For histological types of epithelial OC, the strongest inverse associations with low-dose aspirin use were seen for mucinous and endometrioid tumors [44].

A novel risk factor, the microbial composition change, could be related to initiation and progression of OC via influencing and regulating the local immune microenvironment of fallopian tubes [45]. Using condoms and keeping a good gut and vaginal microbiome, early detection of asymptomatic infections and appropriate treatment of pelvic inflammatory disease, especially if recurrent in younger women, could not only prevent chronic pelvic pain and tubal infertility, could at least theoretically prevent OC.

### *Reduce exposure to environmental toxicants*

Genital talc use that can reach ovaries through fallopian tubes is a controversial cancerogen that seems to have a relative risk (RR) for OC 1.22 (95% CI: 1.13–1.30). Serous carcinoma is the only histologic type for which an association is detected (RR: 1.24; 95% CI: 1.15–1.34). A causal association between cigarette smoking and risk of mucinous ovarian tumors has been established but is also controversial. Endocrine disruptors are substances that could interfere with endogenous hormones and increase OC risk too. Some carcinogenetic mechanisms of endocrine disruptors that can cause OC are known [46]. Unfortunately, there are many methodological reasons that make it very difficult to isolate the net OC cancerogenic effect of the growing multitude of pollutants that interact in a complex way and act in very low doses [47]. Even though the definitive demonstration of specific OC effects of pollution is difficult to demonstrate or quantify by using the precautionary principle, gynecologist should counsel patients to reduce exposure to pollutants, especially if we consider the epigenetic damage in periconceptional exposure that could also affect

**TABLE 1.** Lifestyle advice to reduce ovarian cancer risk.

| *N (%)* | *Variable* |
|---|---|
| • | Normalize weight if overweight or obese |
| • | Increase physical exercise and reduce sedentary |
| • | Eat plenty of vegetables rich in fiber |
| • | Reduce the amount of simple sugars, recommend complex carbohydrates |
| • | Supplement or expose to sunlight if the levels of Vitamin D are low |
| • | Prevent pelvic infections, detect them early and treat them adequately |
| • | Reduce exposure to environmental toxicants |

future generations and/or the effects of pollution on overall health.

## DISCUSSION

Gynecologic consultation aimed to ovarian cancer prevention should not only be limited to early detection and differential diagnosis of adnexal masses. It is pivotal to motivate patients to follow affordable cancer prevention and to promote overall health. We propose to focus counselling on the following important and affordable advice exposed in reducing order of importance and summarized in Table 1. These recommendations are individually not strong enough to specifically reduce OC risk, but they have at least some data that support their preventative effect, and they can at the same time prevent other neoplasms and/or improve overall health. So, when a patient is worried and asks to reduce OC risk, the motivation is a strategic moment to give advice aiming at improving lifestyle for global health promotion at no cost and without risks.

## CONCLUSIONS

Gynecologic consultation provides an excellent opportunity to discuss OC risk and to promote risk reduction strategies that includes body weight normalization, regular exercise, healthy diet largely based on vegetables that have antioxidant and anti-inflammatory properties, low simple sugar diets, adequate levels of Vitamin D, prevention of pelvic infections and low exposure to toxicants. The same lifestyle advices are affordable, and they could also reduce the risk of endometrial and breast cancer and improve overall health without any risk.

### Conflict of Interest:

The Authors declare that they have no conflict of interests.

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