SPECIAL ARTICLE

Lifestyle Factors and the Risk of Endometrial Cancer: A review

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ABSTRACT

Endometrial cancer (EC) is among the most prevalent gynecologic cancers worldwide, experiencing a significant surge in incidence of approximately 60% over the past three decades. Addressing this growing burden involves three primary strategies: EC screening, lifestyle modification, and chemoprevention. Compelling evidence underscores the role of healthy lifestyle changes embracing a nutritious diet, abstaining from alcohol consumption, and regular physical activity (PA) in mitigating not only the risk of cardiovascular diseases but also overall non-cancer mortality in the general population. Moreover, heightened attention from researchers in recent decades has focused on understanding the connection between adopting healthy lifestyle factors and diminishing the risk of various cancers. In the case of EC, current epidemiological findings highlight that modifiable factors such as PA and diet may be linked to a reduced risk of this cancer. This review aims to comprehensively examine and synthesize the latest evidence pertaining to the influence of lifestyle factors and behaviors on the risk of EC, shedding light on actionable insights for risk reduction and preventive measures.

Keywords: endometrial cancer, lifestyle, modification, prevention, risk factor.

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Introduction

Cancer is a leading public health and economic issue worldwide. According to estimates from the International Agency for Research on Cancer, more than 19.0 million newly diagnosed cases of cancer and nearly 10.0 million deaths due to cancer occurred in 2020. Projections indicate that the worldwide incidence of cancer is expected to surge to 28.4 million cases by 2040, representing a substantial 47% increase compared to the statistics recorded in 2020[1].

The burden of cancer expands beyond death from the disease. Individuals affected by a cancer diagnosis experience physical and psychological distress. They also face a decline in their quality of life, which is often related to disease symptoms, investigative procedures, and adverse effects of cancer treatment[2]. The risk factors for cancer are closely associated with population growth, social development, and environmental changes. The evolution of society is inherently linked to lifestyle or behavior changes that contribute to metabolic diseases such as dyslipidemia, hypertension, obesity, insulin resistance, and type 2 diabetes mellitus (DM), potentially increasing the risk of cancer[3-4].

In 2005, information from the World Health Organization revealed that more than one in every three (35%) of the 7 million cancer-related deaths worldwide could be attributed to nine potentially modifiable risk factors, such as lack of physical activity (PA), obesity, cigarette smoking, alcohol use, and an unhealthy dietary pattern. Consequently, the predominant factors influencing global cancer occurrence and mortality are modifiable lifestyle risk factors[5-6]. Nowadays, governmental authorities and prominent non-profit health organizations, including the American Cancer Society (ACS) and the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), have outlined international public health guidelines and recommendations[2, 7-8]. These emphasize a healthy diet, reduced alcohol consumption, achieving a healthy body weight, and physical fitness for the prevention of cancer.

Endometrial cancer (EC) is one of the leading cancers in women around the world, with 417,000 new diagnoses reported globally in 2020[1,8]. The number of diagnoses has increased by approximately 60% in the past three decades due to shifting demographics, specifically an aging population, an uptick in obesity rates, and a decrease in hysterectomies conducted for non-malignant reasons[9]. As we know, established risk factors for elevated EC risk include obesity, unopposed estrogen exposure, and nulliparity[10]. Additionally, lifestyle factors, such as insufficient PA

and a diet high in glycemic content, emerge as significant contributors to EC risk[2, 11-12]. The role of lifestyle modification in the prevention of EC has been established over the past several decades[11]. Growing evidence from both experimental and epidemiological research suggests that lifestyle factors, which can be modified, may impact the risk of EC[11-14]. A systematic review and meta-analysis of four cohort studies and one case-cohort study revealed a negative association between adherence to cancer prevention guidelines (including WCRF/AICR or ACS guidelines) and the risk of EC[13]. In addition, a recent multicentric case–control study demonstrated that higher adherence to the WCRF/ AICR recommendations on body fatness, PA, and diet was associated with about 60 % reduced risk of EC. The study also identified that body weight had the most significant impact on the risk. Therefore, continuing a healthy body weight throughout one's lifetime is the essential suggestion for EC prevention[15]. In this review, our aim is to summarize the most recent evidence regarding the impact of lifestyle factors or behaviors on the risk of EC.

The influence of diet

Bioactive components present in everyday foods have the potential to enhance interactions with chronic inflammation. This may stimulate cell proliferation, inhibit apoptosis, and trigger the secretion of mediators that could lead to carcinogenesis and malignant transformation of cells[16-17]. Numerous investigations have explored the connection between diet and EC risk. For instance, a case-control study in Japan, involving 161 cases and 380 controls, examined the association between food intake and endometrioid EC. The study revealed that a higher intake frequency of vegetables, fish, and boiled eggs was associated with a reduced risk, while higher intake frequency of convenience foods and fried foods showed a positive effect compared to lower levels in the risk of EC[18]. These findings align with a recent meta-analysis of six cohort studies and twenty-one case-control studies, indicating that vegetables

(pooled odds ratio [OR]=0.76), cruciferous vegetables (pooled OR=0.81), dark green and yellow/orange combined vegetables (pooled OR=0.64), and fruits (pooled OR=0.81) were strongly associated with a reduced risk of EC[19].

The International Agency for Research on Cancer has recently reclassified processed meat as a Group 1 carcinogen and red meat as a Group 2A probable carcinogen[20]. Additionally, in relation to the impact of estrogen-containing compounds in animal food on the risk of EC, a systematic review and meta-analysis discovered that the consumption of meat, especially red meat, raises the risk EC[21].

As we are aware, the consumption of sugar-sweetened beverages (SSB) constitutes a significant risk factor for obesity and type 2 DM[22]. However, research attention on the correlation between SSB consumption and the risk of cancer has been limited. The potential mechanism may revolve around their role in promoting tumor cell growth and cell proliferation[22-24]. A population-based cohort study conducted in the United States of America revealed the association between SSB intake and EC risk in 23,039 postmenopausal women. The study demonstrated that elevated consumption of SSB and sugars was linked to a higher risk of type I EC. However, no such association was identified in type II EC[23]. In addition, a recent case-cohort study from Canada also found that SSB intake and/or fruit juice intake are associated with a higher risk of EC[24].

Experimental and laboratory studies have indicated that green tea and coffee possess anticarcinogenic and chemopreventive properties[25-26]. The association between coffee/caffeine consumption and a decreased risk of EC has been confirmed in several previous studies, including a meta-analysis of twelve prospective cohort studies[25-27]. According to the findings of the meta-analysis, increasing coffee intake by four cups per day was linked to a 20% decrease in the risk of EC and a 24% decrease in postmenopausal cancer risk[27]. In certain studies, there has been a connection between green tea consumption and a decreased

risk of EC[25,28], although conflicting findings exist in other studies[26,29].

The influence of obesity

There is evidence that obesity is a significant global health issue and is associated with many metabolic diseases such as hypertension and type 2 DM. Moreover, it is associated with an increased risk and adverse prognostic factors for several types of cancers, including breast, endometrial, and cervical cancers[11, 25, 30-31]. According to findings from a meta-analysis, each increment of 5 body mass index (BMI) units corresponds to a 50% rise in the risk of developing EC[31]. Data from a comprehensive population-based study in Europe revealed that women classified as overweight (BMI 25.0-29.9 kilogram [kg]/meter [m]^2) before the age of 40 had hazard ratios (HR) for EC of 1.70[32]. Furthermore, a substantial nationwide cohort study in Japan indicated that, upon adjusting for potential confounding factors, a BMI exceeding 23.0 kg/m^2 exhibited a linear association with the risk of EC, with the HR per 5 kg/m^2 increase being 1.80. An increase in weight by ≥ +5 kg since the age of 20 was associated with a heightened risk of EC compared to a weight change within the range of -5 to < +5 kg (HR=1.96)[33]. Lastly, a systematic and meta-analysis reported a 60% decrease in the likelihood of developing EC after bariatric surgery, which involves surgical interventions leading to substantial weight loss. This reduction was observed in comparison to controls who did not undergo surgery (relative risk [RR] = 0.4)[34].

The connection between obesity and EC involves a complex system comprising multiple interconnected pathways and mechanisms. Adiposity impacts not just metabolism but is strongly correlated with conditions like hyperlipidemia, insulin resistance, hyperglycemia, and hyperinsulinemia. The components of fat tissue exhibit both pro- and anti-inflammatory characteristics, serving as a source of hormone production and playing a crucial role in endometrial proliferation[31,35].

The influence of alcohol

The association between alcohol intake and EC has been under investigation for many years, yielding inconclusive results. Earlier epidemiological studies have identified a correlation between alcohol consumption and increased levels of circulating estrogens in women, implying a potential elevation in the risk of EC[36-37]. Nevertheless, moderate alcohol intake has been linked to beneficial effects on the adiponectin inflammatory marker and insulin sensitivity, potentially reducing the risk of EC[38]. Despite these findings, the majority of epidemiological and meta-analysis studies consistently report no association between alcohol consumption and EC risk[25, 39-42].

The influence of physical activity

Growing epidemiological evidence suggests that engaging in PA could lower the risk of cancer, including EC[11-12, 14,43]. Moore et al. conducted a meta-analysis of nine prospective studies to determine the association of PA and EC risk. They discovered that recreational PA was significantly linked to a decreased risk of EC, with active women having a roughly 30% lower risk than inactive women[14]. A large-scale nationwide cohort study in Japan suggests that compared to women who were mainly sitting at the worksite, those who were mainly standing (HR=0.79) and moving (HR=0.46) had a lower risk (P for trend=0.042)[33]. Additionally, recent data from a systematic review and meta-analysis of fourteen studies reported a 55% increased risk of EC among individuals with higher levels of total sedentary behavior (RR=1.55), a 22% increase among those with higher levels of occupational sedentary behavior (RR=1.22) and a 34% increase with borderline significancy among those with higher levels of leisure-time sedentary behavior (RR=1.34). The overall increased risk disregarding specific domains was 27% (RR=1.28)[44]. Current recommendations from the ACS for diet and PA for cancer prevention suggest that adults should engage in 150-300 minutes of moderate-intensity PA per week, or 75-150 minutes of vigorous-intensity PA, or an equivalent combination; achieving or exceeding the upper limit of 300 minutes is optimal[2].

Several hypotheses have been proposed to elucidate the reduced risk of EC associated with PA. PA may contribute to the reduction of serum estradiol levels and the increases of sex hormone binding globulin, the binding protein for estradiol. Additionally, it might lead to lower levels of reactive oxygen species, enhanced immune function, reduced inflammation, and improved insulin sensitivity[14, 43]. These beneficial effects of PA may also be mediated through prevention of weight gain[14].

The influence of smoking

It is now well established that cigarette smoking increases the risk of developing cardiovascular and respiratory tract diseases. Cigarette smoking also increases the risk of various cancers, including lung, nasopharynx, bladder, and cervical cancers[45]. Conversely, cigarette smoking is associated with a lower risk of EC[25, 46-47]. A meta-analysis of ten prospective and twenty-four case-control studies reported that overall, smoking was statistically significantly associated with 18% and 29% reduced risks of EC in prospective and case-control studies, respectively[46]. Dimou et al. recently conducted an extensive multicenter observational study to thoroughly investigate the connection between smoking and the risk of EC. Their findings in the observational analysis revealed an association between a lifetime amount of smoking and regular smoking with a lower risk of EC. However, in the Mendelian randomization analysis, considering BMI and a genetic predisposition to a higher lifetime amount of smoking, there was no association observed with EC risk[47].

The potential mechanism that could explain this association involves antiestrogenic effects[25,46]. Smoking is also linked to an earlier age at menopause, and as a result, it may reduce the risk of developing EC due to decreased exposure to endogenous circulating estrogen levels[47].

Conclusion

EC stands out as a major concern in women's health, marked by a growing number of diagnoses, investigations, and treatments attributed to the increase in life expectancy and the rise in obesity rates. Additionally, unhealthy lifestyle behaviors, such as a lack of PA and a diet or beverage high in sweet sugar content, emerge as significant contributors to EC risk. Therefore, it is prudent to provide lifestyle recommendations focused on mitigating EC risk, such as increasing PA, maintaining a healthy body weight, and adopting a balanced diet rich in vegetables and fish, to all women. Discussing specific preventive strategies during counseling and personalized risk assessment is crucial. Moreover, implementing effective cancer prevention recommendations or guidelines for everyone, including women, may lead to a lower incidence of EC.

Potential conflicts of interest

The authors declare no conflicts of interest.

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