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Review Article

Dietary and Lifestyle Strategies for Endometrial Cancer Prevention: Emerging Evidence and Unanswered Questions

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Abstract

Endometrial cancer is a common malignant tumor of the female reproductive system, and its incidence is increasing worldwide. The underlying causes of endometrial cancer are multifactorial. In recent years, the role of diet and lifestyle has received considerable attention and has become a key area of research for cancer prevention. Available literature suggests that different dietary patterns, such as the Mediterranean diet or a plant-based diet, along with moderate physical activity, are associated with a reduced risk of this cancer. Despite these findings, significant gaps in knowledge remain, particularly regarding the specific foods, lifestyle choices, and mechanisms of action that can help mitigate the risk of cancer. Furthermore, the effects of cultural and genetic differences among subpopulations make this issue even more complex. In this context, this review aimed to assess the existing literature on the potential role of diet and lifestyle factors in preventing endometrial cancer, evaluate the available data, and highlight areas that require further investigation to provide concrete evidence and recommendations for prevention.

Introduction

Recent global cancer statistics reveal endometrial cancer (EC) as the sixth most common malignancy in women, with 420,368 new cases and 97,723 deaths worldwide in 2020.[1] Notably, incidence rates have shown a paradoxical increase of 1.5% annually since 2010, despite advancements in diagnostic modalities, particularly among premenopausal women in developed nations. This epidemiologic trend is closely linked to obesity, and population-attributable risk analyses estimate that 40–60% of cases may be preventable through lifestyle changes,[2] especially in diet and nutrition, which are two primary modifiable factors. Likely, engaging in positive dietary practices along with a physically active lifestyle may help reduce the risk of developing EC, but more research is needed to understand how this protective effect is achieved. Epidemiological studies have demonstrated that obesity is a risk factor in over 65% of samples involving obese women with EC and other overweight women.[3] Diets associated with obesity may contribute to a person's risk for EC, highlighting a strong association between diet and cancer risk. Studies show that individuals who follow a Mediterranean diet, rich in fruits, vegetables, whole grains, and healthy fats, tend to have a significantly lower risk of EC. These findings strengthen the argument for how diet quality can help prevent cancer and underscore the importance of healthy eating for disease prevention.[4] The dynamic between nutrition, physical activity, and EC is intricate. Of particular interest is the intake of long-chain omega-3 polyunsaturated fatty acids, which has been shown to increase the risk of EC in overweight and obese women.[5] Another important factor influencing cancer risk is inflammation and insulin resistance. High consumption of sugar and fat may potentially contribute to chronic inflammation and insulin resistance among obese individuals.[6] Research indicates that abundant sugars and fats in one's diet may be linked to a higher susceptibility to EC.

Regular physical activity is believed to lower the risk of EC, consistent with substantial research linking higher levels of physical activity to a reduced risk of developing EC.[6,7] Additionally, lifestyle change is heavily influenced by psychological and social factors. Evidence suggests that mental health is closely associated with physical activity levels.[8]

Dietary and lifestyle interventions have shown promise in reducing the risk of EC; however, the underlying mechanisms and influencing factors warrant further investigation. This review aimed to analyze existing epidemiological data to explore the complex relationship between diet, lifestyle, and the prevention of EC, while also offering guidance for future research endeavors.

Keywords: Lifestyle intervention; Dietary patterns; Endometrial cancer; Hereditary syndromes; Prevention; Research evidence; Nutrient debate; Dose-effect.

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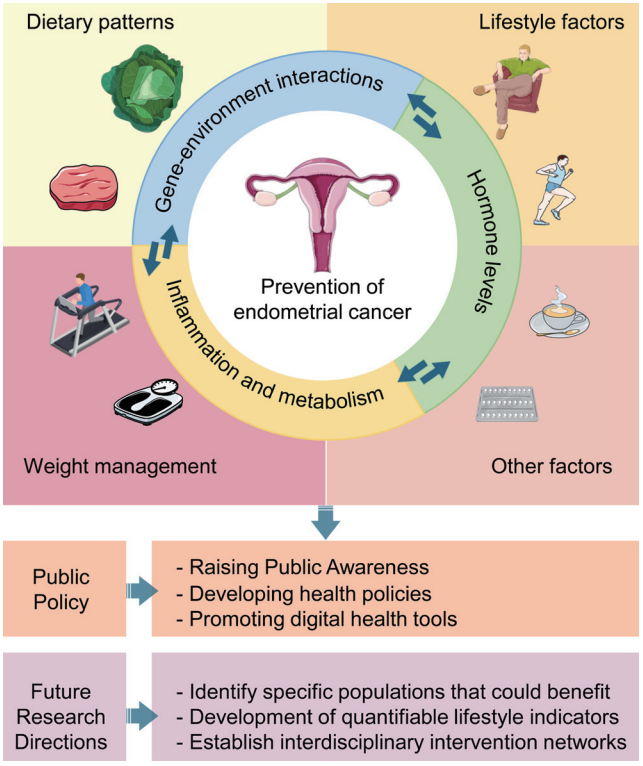

Fig. 1. Risk factors and multidimensional prevention framework map.

Our focus will encompass the role of various dietary components, the effects of lifestyle modifications, and strategies for promoting healthy behaviors through effective public health policies (Fig. 1).

Evidence base

A comprehensive literature search was performed using prominent databases, including PubMed, Cochrane, Embase, and Web of Science. The search was limited to studies published between 2014 and December 8, 2024. Key terms such as "EC," "lifestyle," "dietary exposure," "prevention," and their combinations were employed to identify high-quality articles. PubMed Medical Subject Headings were used to validate the keywords, and a manual review of references from retrieved articles and related systematic reviews was conducted. The selected articles were managed using EndNote and included full-text, English-language quantitative studies with relevant keywords published within the specified timeframe. The investigation focused on all prevention factors. Case reports, commentaries, letters to the editor, case series, and animal studies were excluded. Ethical guidelines were strictly followed throughout the research process.

The complex interplay of diet, lifestyle, and endometrial cancer prevention

Is the role of dietary patterns over- or underestimated?

Numerous studies have demonstrated that cancer risk is influenced by dietary patterns, lifestyle choices, and an individual's metabolic status, collectively impacting cancer risk. Notably, obesity and metabolic syndrome are recognized as significant risk factors for EC and are closely associated with dietary habits.[9] While there is ongoing debate about the impact of dietary patterns on EC, their significance remains crucial. Many studies suggest that adhering to a balanced diet, such as the Mediterranean diet,[10] which is rich in fruits, vegetables, whole grains, and healthy fats, can significantly lower the risk of developing EC. However, some researchers argue that dietary patterns are given excessive importance. For instance, one study claimed that while people's diets may contribute to cancer, they are likely less significant than genetic and environmental factors. The relationship between diet and cancer is complex, with a case-control study finding a positive correlation between a negative diet index and EC.[10] Additionally, the Women's Health Initiative reported that a marker of inflammation, C-reactive protein, was associated with EC risk.[11] Lowering diet index through diets that include plenty of vegetables and coffee reduces cancer risk, while those rich in animal fat and protein increase it.

In recent years, researchers have shown growing interest in the relationship between dietary patterns and EC. Specifically, the Mediterranean diet is believed to help prevent certain cancers. However, the "generalizability" of these diets is often taken too lightly, failing to consider the differential effects among various populations. The Mediterranean diet includes a variety of plant foods, healthy fats (particularly olive oil), and moderate fish consumption. People following this diet tend to have a lower risk of several cancers, including EC. A systematic review estimated that following the Mediterranean diet leads to a 13% relative risk reduction for EC.[4] However, efficacy varies depending on an individual's genetic background, personal lifestyle, and socioeconomic status. For example, obese women and specific ethnic groups may respond differently to the Mediterranean diet. The ketogenic diet (KD), which is high in fat, moderate in protein, and very low in carbohydrates, has also shown potential in weight management and insulin sensitivity, suggesting it could be a strategy for EC prevention. Obesity and metabolic syndrome increase the risk of EC, and insulin levels directly affect EC development. The ketogenic diet can lower these risks by promoting weight loss and improving insulin resistance.[12] It has been shown to reduce insulin secretion, aid in weight management, and improve insulin sensitivity, thus potentially preventing EC.[9] However, the potential long-term risks, such as nutritional imbalances, liver abnormalities, and kidney damage, require attention.[13] Healthcare professionals should be consulted before implementing KD. The diabetes risk reduction diet (DRRD), which is high in fiber, low in sugar, and includes healthy fats with moderate protein intake, aims to reduce the incidence of diabetes and related cancers. Diets high in sugars and fats potentially increase the risk of EC.[14] Studies show an inverse association between following a DRRD and the likelihood of EC among women with a diet high in fiber and low in sugar.[15] However, the DRRD is less effective among women of certain races, ages, and obesity categories. Some research suggests that women with obesity tend to adhere more to the DRRD and experience a greater reduction in EC risk, indicating the diet works better in the presence of metabolic illness. An Italian case-control study reported that those who followed the DRRD and consumed more vegetables experienced a significantly lower risk of cancer.[16] Soy isoflavones play a significant role in a whole food diet and have been termed a "double-edged sword". Phytoestrogen soy isoflavones have been linked to a lower risk of EC in certain populations with high isoflavone consumption.[17] However, concerns remain that soy isoflavones may increase the risk of cancer recurrence,[18] making their use among cancer patients controversial. Clinical data show a link between isoflavone consumption and an increased risk

of cancer recurrence in patients undergoing isoflavone therapy.[8] The current evidence regarding soy isoflavones is characterized by conflicting findings, with studies indicating both protective effects and potentially harmful consequences. Therefore, the use of soy isoflavones as dietary supplements should be approached with caution, particularly for women with a family history of EC or other hormone-related conditions. Future studies should investigate how different populations respond to soy isoflavones to develop personalized dietary recommendations.

These paradoxes highlight the importance of considering a person's health status, cancer stage, and treatment plan when developing dietary measures to prevent EC. Soy isoflavones may be harmful when consumed by cancer patients, so further research is needed on the role of diet in cancer pathology and prevention, especially regarding how to optimally use nutrients in everyday clinical practice.[19] Additionally, investigating cancer-related dietetic patterns faces challenges such as ethnic background, lifestyle, and socioeconomic class, which complicate the analysis of the diet-cancer linkage. Such considerations can bias the accuracy of results, particularly in high-risk groups with different caloric intake priorities.[20] Cultural and geographic differences significantly influence dietary patterns; for instance, populations in the Mediterranean region typically have better access to fresh fruits and vegetables.[9,19] Thus, it is unreasonable to treat the Mediterranean diet or Dietary Reference Intake Recommendations as a one-size-fits-all primary prevention tool for all populations.

The body mass index (BMI) is frequently regarded as a significant confounding factor in research exploring the link between diet and EC. Studies from the Nurses' Health Study and the Nurses' Health Study II cohort have demonstrated a strong association between the Empirical Dietary Inflammatory Pattern and the Empirical Dietary Index for Hyperinsulinemia scores and the incidence of EC. Notably, BMI accounts for 84–93% of this relationship, indicating that obesity may play a crucial role in shaping the connection between diet and EC.[21] Obesity affects hormone levels and increases the risk of EC through mechanisms such as chronic inflammation and metabolic disorders. Regional differences increase the association between diet and EC. In Asian populations, this relationship may differ from that in Europe and the United States due to generally lower rates of obesity. A prospective study conducted by the Japanese Center for Public Health found that, in their study population, the association between a high glycemic index diet and EC was not significant, possibly due to the lower overall prevalence of obesity in the region.[22] Therefore, region-specific studies appear necessary to fully understand the intricate interactions between diet, BMI, and EC in different cultural contexts. In addition, the role of socioeconomic factors in influencing diet and EC risk is also worth exploring. The relationship between BMI and EC is further complicated by the fact that in more developed regions, residents usually have greater dietary choices and access to healthier food options. In economically disadvantaged areas, however, residents often face limited dietary choices, which may lead to higher rates of obesity and an increased risk of EC. To better understand the association between dietary patterns and EC, future studies should incorporate socioeconomic factors into the analysis and focus on the composition and quality of the diet.[21] Researchers should also focus on determining the effects of different dietary compositions on the risk of EC, considering the potential interference of BMI, and employ standardized dietary assessment tools to reduce confounding factors. Clarifying the causal relationship between dietary patterns and the risk of EC will help in understanding the role of diet in cancer prevention. Various factors, including BMI, cultural differences, socioeconomic status, and the quality of dietary components, influence this relationship. Future research needs more high-quality studies to elucidate the mechanisms and magnitude of these effects. By focusing on individual differences and evaluating health outcomes in different populations with the same dietary patterns, researchers can develop more effective prevention strategies while increasing public awareness of the relationship between diet and health.

Tobacco use, alcohol consumption, and psychological factors have been identified as significant lifestyle elements that contribute to the risk of EC. The relationship between smoking, alcohol consumption, and EC is not uniform. Several epidemiological studies have demonstrated a negative correlation between smoking and the risk of EC, a phenomenon that may be attributable to the impact of smoking on estrogen metabolism.[23] However, the potential impact of smoking on endometrial health may be indirect, exerted through its influence on inflammatory response mechanisms and cellular stress pathways within the body.[24] The effects of alcohol consumption are relatively more complex. A recent multicenter prospective study reported a correlation between alcohol and EC, where mild alcohol intake was negatively correlated with EC risk. This effect appeared to be stronger in obese women. Higher alcohol intake did not provide an additional therapeutic benefit in treating EC, and the study hypothesized that obese women tend to be insulin-resistant and have higher levels of insulin. Alcohol may help improve these conditions.[25] However, dose-response meta-analyses of prospective studies have found that alcohol consumption was not associated with EC, regardless of beverage choice and alcohol consumption level.[26] In a small cohort study, smoking and alcohol consumption after EC diagnosis were found to be unrelated to disease-free survival, while pre-diagnostic smoking and alcohol consumption were not associated with any of the outcomes.[27] In a 2024 Mendelian randomization study, genetically predicted lifetime smoking index, alcohol frequency, BMI, T2DM, and fasting insulin were found to increase the risk for EC.[28] Poor psychological health, such as depression and anxiety, strongly correlates with a worse cancer prognosis. Psychological stress can influence the development and progression of cancer by affecting the immune and endocrine systems.[8] Lack of social support may also exacerbate mental health problems, further affecting the quality of life and recovery process of cancer patients.[29] Smoking, alcohol consumption, and psychological factors play a complex role in EC development, with further research needed to confirm their overall effect. Therefore, interventions, education, and lifestyle modifications can help prevent EC and improve patients' quality of life.

Distinct preventive paradigms: Hereditary syndromes vs. sporadic endometrial cancer

Data on lifestyle-associated hormonal and medical factors among women with EC who carry the Lynch syndrome (LS) mutation are limited. These individuals tend to have a lower mean age of disease onset and a lower body mass index compared to those without LS.[30,31] A recent review article on EC prevention modalities in patients with LS showed no association between weight loss and EC. In terms of dietary habits, multivitamin and folic acid supplementation may reduce the risk of EC, while alcohol consumption was associated with the risk of rectal cancer but not significantly with EC.[32] A 2024 international cross-sectional survey investigated modifiable risk factors for cancer in patients with LS, including BMI, physical activity, smoking, and alcohol consumption.[33] The study recommended maintaining a healthy weight, engaging in at least 150 m of moderate-intensity physical activity per week,

avoiding smoking and alcohol, and considering the use of aspirin for chemoprevention. A study on the role of aspirin in the prevention of EC in LS demonstrated that daily administration of 600 mg of aspirin led to a 52% reduction in the risk of LS-associated EC in individuals carrying the MLH1 gene mutation, with this effect observed after at least two years of treatment.[34] Aspirin may reduce EC risk by inhibiting estrogen biosynthesis through the COX-2/PGE2 pathway, and studies have shown a strong correlation between frequent aspirin use and risk reduction.[35] In addition, oral contraceptives (OCs) or progestins alone may also reduce the risk of EC.[36]

While improvements in lifestyle have been demonstrated to reduce the risk of certain cancers, the influence of genetic factors is more pronounced in patients with LS. Individuals with LS remain at a higher risk for EC even when they adopt a healthy lifestyle.[37] Thus, the impact of lifestyle changes may be overshadowed by genetic factors in individuals with higher genetic susceptibility. Existing clinical guidelines, while promoting healthy diets and lifestyles, lack specific guidance for patients with LS, which limits their practical implementation by clinicians.[38]

In summary, although lifestyle and dietary improvements have potential benefits in the prevention of EC, their effectiveness in patients with LS is influenced by genetic factors and individual differences. Future studies should molecularly stratify patients with hereditary oncogene mutations. A comprehensive assessment based on individual genomic characteristics, living environment, and psychological status will help develop more effective preventive measures.

The 'reductionist' vs. 'holistic' nutrient debate

Reductionist: The breaking down of complex systems into isolated parts, such as separating nutrients to study their individual functions. Holistic: Treats food as an indivisible whole, emphasizing that the whole is greater than the sum of its parts (1+1 >2).[39] The debate between "reductionist" and "holistic" approaches in nutrition affects our understanding of dietary practices. "Reductionist" focuses on individual nutrients with the aim of developing dietary guidelines based on the health effects of these specific components. Common studies on minerals, trace elements, and vitamins aim to clarify their direct and preventive effects on cancer, emphasizing recommendations for the intake of specific foods or dietary supplements rich in these nutrients. In contrast, "holistic" emphasizes food combinations and overall dietary patterns, arguing that the impact of a single nutrient cannot be fully understood without considering the broader dietary context. This perspective promotes a balanced diet that includes a variety of foods and recognizes the interactions between different nutrients. This debate influences not only nutrition research but also public health policies and individual dietary choices.

Proponents of reductionist research argue that understanding specific nutrients can help prevent and treat diseases. Studies indicate that micronutrients like selenium and zinc play crucial roles in cancer prevention.[40] Fine-tuning research can uncover the connections between nutrients and gene expression, providing a scientific foundation for personalized nutrition.[41] However, recent nutritional studies focusing on individual nutrients often yield conflicting results, particularly regarding nutrients such as vitamin C and selenium. Some studies suggest that vitamin C may lower the risk of certain malignant neoplasms, including EC,[42,43] while others indicate it may increase risk,[16] suggesting that individuals at high risk should avoid vitamin C supplements. These contradictory findings underscore the limitations of studies that focus solely on single nutrients, especially when they overlook the importance of overall dietary patterns and their cumulative effects on health.

The limitations of reductionism must be discussed when examining the role of diet and lifestyle in EC prevention. Reductionism simplifies complex biological processes, ignoring interactions between various individual factors. Although vitamin C is often thought to protect against free radical damage, recent studies have found that under certain conditions, vitamin C can exhibit pro-oxidant effects. This suggests that studying vitamin C in isolation may yield misleading results if its role in the broader diet and lifestyle is ignored.[44] Moreover, the impact of nutrients on EC prevention cannot be assessed in isolation. The influence of individual dietary components is shaped by population, cultural, environmental, and genetic factors. For instance, the health effects of fatty acid intake can differ based on their type and source. A study involving 87,360 participants indicated that higher consumption of specific long-chain omega-3 polyunsaturated fatty acids was associated with a 15–23% reduction in EC risk.[44] Conversely, another study found that high dietary intake of docosahexaenoic acid was linked to a 9% increase in EC risk.[5] This implies that different doses of omega-3 fatty acids may have distinct effects on cancer risk, and determining the ideal amount is crucial for formulating dietary guidelines and prevention strategies.

Coffee consumption exhibits a dose-dependent protective effect against certain health issues, particularly when three to four cups per day are consumed. However, this effect can be influenced by brewing methods and additives.[45] Similarly, research on trace elements like selenium is inconsistent, with some studies suggesting an anti-cancer effect,[46] while others raise concerns or show no relationship with gynecological cancers.[47,48] Selenium and quercetin have shown synergistic cytoprotective and radioprotective effects in endometrial adenocarcinoma cells,[49] indicating that a single nutrient may be influenced by other nutrients and dietary components.[50] Therefore, evaluating the effect of a nutrient in isolation, without considering its role within the broader dietary context, can lead to oversimplified conclusions.

Translating laboratory evidence into practical dietary recommendations presents a significant challenge. For instance, laboratory studies investigating the anticancer properties of plant extracts,[51] such as enterolactone, have shown promising results. However, the limited *in-vivo* and *in-vitro* studies supporting enterolactone's strong anti-cancer effects against various types of cancer, including EC, are often conducted in highly controlled settings. Consequently, these findings may not be directly applicable to clinical practice or everyday dietary choices.[52] While certain plant compounds demonstrate notable anticancer activity in laboratory tests, their absorption and metabolism in humans can differ significantly, making it difficult to convert these findings into specific dietary guidelines.

A holistic perspective in diet research emphasizes the importance of considering not only individual nutrient intake but also the interactions between foods and their collective impact on health.[4] This comprehensive view is further supported by public health policies, which have evolved to reflect a more integrated approach.[53] For instance, dietary guidelines in various countries have transitioned from single-nutrient recommendations to promoting overall dietary patterns and lifestyles.[54] In the United States, guidelines encourage individuals to diversify their food choices, advocating for the consumption of whole grains, vegetables, and fruits, rather than merely focusing on the reduction of specific nutrients.[20]

Many studies support a holistic perspective on dietary patterns, but practical application faces challenges due to consumer

influence by advertising and marketing,[55] which can lead them to overlook the importance of a comprehensive dietary approach. In addition, factors like cultural background, economic status, and personal preferences may also influence an individual's dietary choices to varying degrees, creating barriers to the effective implementation of a holistic dietary pattern.[56] Effective dietary recommendations must consider an individual's health status, lifestyle, cultural background, and the availability of food resources. Studies have shown that interventions based on holistic dietary patterns like the Mediterranean diet or plant-based diets may be more effective in reducing the risk of EC than focusing on individual nutrients.[15] Future research should prioritize the integration of laboratory findings with real-world dietary practices to develop effective dietary recommendations.

In conclusion, the current debate on "reductionist" vs. "holistic" nutrients has important theoretical and practical implications for nutrition research. Research focusing on reductionism can enhance the understanding of specific nutrients, while holistic dietary strategies have demonstrated broader effectiveness in preventing chronic diseases and improving public health. Future research should balance these two approaches, using a holistic perspective first, complemented by a reductionist approach.[57] A shift in focus is required in human nutrition, emphasizing the holistic implications of specific foods and food combinations,[50] while still examining the role of individual nutrients. This two-pronged approach can lead to more effective nutritional interventions and health policy development. The limitations of reductionism reveal that oversimplification should be avoided in research and practice. Translating laboratory findings into practical recommendations is challenging, so individual differences and the broader dietary context must be considered when developing dietary guidelines. By addressing these aspects, we can provide stronger scientific guidance for EC prevention.

The "dose-effect" paradox of lifestyle interventions

There is increasing interest in understanding how exercise can prevent EC.[28,58–62] The "dose-effect" paradox has become an important topic in the discussion of the impact of lifestyle interventions on disease. This paradox reveals that the effects of lifestyle changes do not always match their intensity. Specifically, high-intensity interventions do not always result in the expected health benefits, while low-intensity interventions sometimes result in significant health improvements. This phenomenon has been confirmed by numerous studies, particularly in controlling chronic diseases like obesity,[63] cardiovascular disease,[64] and diabetes.[65]

Individual differences, such as genetic background, psychological status, and socioeconomic factors, significantly impact the effectiveness of lifestyle interventions. A study of people with hypertension found that adherence to healthy eating and increased physical activity varied among participants.[66] The type and content of the intervention also shape the "dose-effect" relationship. While adherence to a Mediterranean-style diet and moderate physical activity can reduce the risk of chronic disease, overly restrictive diets or excessive exercise can be harmful. Severe restriction of calorie intake may lead to metabolic disorders and disruption of normal body functioning.[67] Exercise intensity is crucial in influencing cancer risk, but the relationship is complex and varies among populations.[68] This complexity calls for a reevaluation of the "optimal intensity of intervention". Specifically, studies suggest that engaging in at least 15 MET-hours weekly can lower EC risk.[69] However, this protective effect diminishes when considering BMI, particularly in obese women. This implies that obese individuals may need more vigorous exercise to lower their risk. The link between obesity and EC appears to be multifaceted, potentially involving hormone levels, metabolic conditions, and inflammatory responses.[9,70]

Developing lifestyle intervention strategies requires consideration of both the intensity of the intervention and the individual's adaptability and differences, which can help prevent the negative effects of over-intervention. Psychological factors also play an important role in intervention success. Motivation, expectations, and psychological state can greatly influence intervention effectiveness. Individuals with high expectations are more likely to comply and adopt positive health behaviors, while those with low expectations may disengage due to disappointment.[71] Psychological support and interventions can also help overcome psychological barriers and improve intervention effectiveness. The "dose-effect" paradox further illustrates the complexity and variability of lifestyle intervention research, as the results of different studies may vary greatly depending on factors such as study design, participant characteristics, and the specifics of the intervention. Therefore, researchers must consider individual differences, cultural background, and psychological factors when designing intervention studies to develop more targeted and effective strategies.[20]

The effects of sedentary behavior on cancer are significant. Studies have found that 6–10% of EC cases can be attributed to prolonged sitting,[70] while 7.5–15 MET-hours weekly of leisure-time physical activity reduces cancer risk.[72] A study in the United States found a positive correlation between prolonged sitting and the risk of colon and EC.[73] Leisure sedentary behavior, including television watching, non-work computer use, and driving, was linked to a 30% increase in EC risk.[74] A recent meta-analysis of 14 studies showed a 28% higher risk of EC with higher sedentary behavior adjusted for physical activity. These findings indicate that higher levels of sedentary behavior increase EC risk. Further research should confirm the link through objective measurements of sedentary behavior, as well as examine how physical activity, body fat, and sedentary time interact in relation to EC risk.[75]

Measurement bias poses a significant challenge in EC research, particularly when studies depend on self-reported data. The accuracy of self-reports can be compromised by various factors, ultimately affecting the reliability of study findings. Evidence suggests that participants frequently report healthier eating habits and greater exercise frequency to align with societal expectations. In contrast, objective monitoring tools, like wearable devices, can yield more precise data. These devices are capable of tracking participants' activity levels and physiological indicators in real time, thereby minimizing the influence of subjective bias. Consequently, future research should prioritize the incorporation of objective monitoring methods to enhance the accuracy and reliability of the collected data.[76]

Promoting physical activity and reducing sedentary behaviors are effective strategies for cancer prevention, operating through various mechanisms.[28] Exercise offers multiple beneficial effects at systemic and tissue-specific levels, including improving redox homeostasis, enhancing immune function, decreasing inflammation, and increasing insulin sensitivity.[62,69] An active lifestyle can also mitigate the activation of abnormal cancer-related gene expression programs by boosting redox buffering capacity.[62] The role of exercise in protecting against EC by enhancing insulin sensitivity is particularly worthy of in-depth exploration. Research indicates a strong link between obesity, insulin resistance, and the development of EC, suggesting that improving insulin sensitivity could lower cancer risk.[9] While exercise is crucial in enhancing

insulin sensitivity, current studies have not thoroughly investigated the specific mechanisms that connect exercise to EC. Therefore, further mechanistic studies are essential to clarify how exercise may reduce the risk of EC by influencing insulin sensitivity and other metabolic pathways.

In summary, the "dose-effect" paradox of lifestyle interventions emphasizes the importance of personalized intervention strategies to enhance health outcomes. The relationship between exercise, sedentary behavior, and EC prevention varies among different populations, indicating the need for tailored studies. Current research on EC faces challenges such as measurement bias and a lack of mechanistic studies. Future investigations should implement more objective monitoring techniques and examine the connection between exercise and insulin sensitivity, thereby providing a stronger scientific foundation for developing effective preventive measures.

Controversy over contraceptive drugs and birth control devices in the prevention of EC

Proper contraception plays a crucial role in lowering a woman's risk of EC and protecting the uterine lining, which is essential for preserving fertility. Research indicates that the risk of EC is notably reduced among women who use OCs.[77] Long-term use of OCs has been associated with a reduced risk of EC,[78] with some studies suggesting a reduction in risk by 40%,[79] and an even lower EC risk (by 50–60%) in women who engage in low to moderate physical activity.[80] A large retrospective study demonstrated that the protective effects against ovarian and EC remain significant for up to 35 years after the last use of OCs. Overall, the evidence suggests that OCs can dramatically lower women's risk of ovarian and EC, while their impact on the lifetime risk of breast cancer appears to be limited.[81] Although there are indications of increased breast cancer risk among women currently using OCs, the benefits of reduced risks for ovarian, endometrial, and likely colorectal cancers are associated with longer durations of contraceptive use.[82] The most notable reductions are seen in women with pre-existing health issues like smoking and obesity. Although OCs may lower EC risk in obese women, obesity itself poses an independent risk factor for venous thromboembolism, complicating the assessment of the overall risk-benefit ratio. The American College of Obstetricians and Gynecologists advises caution when prescribing estrogen-containing contraceptives to individuals with a BMI of 30 or higher, as this population is already at an elevated risk for EC.[80] Therefore, it is crucial to evaluate the advantages and disadvantages of using combined OCs as a preventive strategy against EC, particularly in light of other potential health issues that may arise.

The utilization of intrauterine devices (IUDs), including those without embedded progestins, has been shown to provide protective benefits, with a 19% reduction in risk for women who have ever used an IUD compared to those who have never used one.[83] The levonorgestrel-releasing intrauterine system (LNG-IUS) appears to be an effective strategy for preventing obesity-driven EC, particularly in women at the highest risk.[84,85] Research indicates that women who have ever used LNG-IUS have a significantly lower risk of developing ovarian and EC.[86] However, an emerging hypothesis suggests that the use of the LNG-IUS device may alter the structure of the cervical-endometrial flora, potentially leading to an increase in the pro-inflammatory bacterium Prevotella, which could heighten the risk of cancerous changes.[87] Critics of this hypothesis argue that the evidence is primarily based on animal studies and that progesterone itself possesses anti-inflammatory properties, meaning that changes in bacterial flora may not necessarily lead to disease.[88] Preliminary studies have also indicated that the microRNA expression profiles in endothelial cells of LNG-IUS users differ from those of users of combined OCs, suggesting that there may not be long-term epigenetic regulatory effects.[66] As a result, the continuation of the protective effects after stopping the medication remains a topic of debate. Nonetheless, these controversies present opportunities for advancing precision prevention strategies. They highlight the evolution of both IUDs and LNG-IUS from simple contraceptive methods to strategic tools in cancer prevention, reflecting significant medical advancements. Future research directions may include the development of biomarker panels, such as endometrial microRNA profiles, to better predict individual risk-benefit ratios, the design of adaptive clinical trials to evaluate multiple outcomes simultaneously, and the creation of patient decision aids to clarify these controversies and encourage shared decision-making among patients and healthcare providers.

Possible pathways to personalized prevention

Stratified interventions focusing on metabolic phenotypes, such as insulin resistance and inflammatory status, are an emerging direction in personalized prevention strategies. This approach aims to develop more targeted interventions by comprehensively analyzing an individual's metabolic profile. It is centered on the recognition that physiological, genetic, and environmental factors vary from person to person and can significantly impact the development of disease. For example, insulin resistance and inflammation are key factors strongly associated with several metabolic diseases, including type 2 diabetes and EC. By implementing stratified intervention strategies that take these metabolic phenotypes into account, healthcare providers can effectively identify at-risk populations and provide personalized preventive measures that are better suited to individual needs.

Studies targeting specific obese subgroups have shown that the effect of docosahexaenoic acid on EC is predominantly seen in overweight women, highlighting the importance of an individual's BMI in assessing the risk of the disease.[89] In addition, changes in the risk associated with hormone replacement therapy (HRT) have also been associated with BMI, suggesting that the use of HRT should consider an individual's weight status.[90] These insights imply that tailored prevention strategies for individuals with different weight ranges should factor in their metabolic profiles to improve the effectiveness of interventions.

Genetic background has a strong influence on personalized prevention strategies, particularly in patients with LS, who may be less responsive to hormonal contraceptives for EC prevention compared with the general population.[91] Special caution is needed when considering long-term HRT for patients with LS, as their unique genetic profile can result in a different response to HRT compared to the general population.[92] This highlights the critical role of genetic-environmental interactions in disease prevention.

Despite the theoretical promise of personalized prevention, several challenges hinder its practical application. One significant issue is the evident research gaps in precision medicine, particularly the scarcity of large cohorts that integrate multi-omics data, such as metabolomics and genomics. Most current studies focus on single-omics data, which limits a comprehensive understanding of individual metabolic profiles.[71] Additionally, barriers in clinical practice present another obstacle that cannot be overlooked. A pressing concern is how to identify high-risk subgroups at a low cost. For instance, the screening value of inflammatory markers like C-reactive protein, interleukin (IL)-6, and IL-1 receptor antagonist has not been sufficiently validated,[93] and there is a notable

lack of effective tools to assist clinicians in implementing these screenings. Therefore, establishing effective screening mechanisms and tools is crucial for advancing personalized prevention strategies.

In clinical practice, healthcare providers can implement personalized prevention strategies through individualized assessments of patients' dietary habits, lifestyle, cultural background, socio-economic status, and personal health goals. This includes the development of a tailored dietary and lifestyle intervention plan that ensures feasibility and sustainability, considering the patient's specific needs and preferences. Ongoing support and education are integral to the intervention, ensuring patient participation and adherence to recommended lifestyle changes over time, and promoting the maintenance of a healthy lifestyle through regular follow-up visits and educational sessions. Dissemination of modern information on nutrition and physical activity can help address barriers to lifestyle changes. Digital health technologies, such as apps and wearable devices, are critical, facilitating patient monitoring and management of diet and exercise, improving adherence and intervention outcomes. Multidisciplinary teamwork, with dietitians, public health specialists, and gynecologic oncologists collaborating, is critical to providing patients with a comprehensive prevention strategy.

In summary, a viable approach to personalized prevention necessitates closing the gap between theoretical research and clinical practice. This involves accurately identifying and intervening in individual metabolic profiles through the integration of multi-omics data, as well as refining screening tools and mechanisms. Future research should prioritize investigating the practical application of these personalized strategies within clinical settings to enhance both the efficiency and effectiveness of disease prevention efforts.

Limitations of current evidence

A substantial body of research has investigated the association between dietary patterns, lifestyle, and EC risk. However, methodological heterogeneity arises from discrepancies in study design, sample selection, data collection, and analysis methods. Some studies exclusively included samples from specific regions and populations, thereby restricting the generalizability of their findings. Additionally, the impact of confounding factors, such as obesity and diabetes mellitus, was inadequately addressed during the study process, potentially resulting in biased findings. The use of self-reported data in some studies may introduce memory and social desirability biases, compromising the accuracy of findings. Furthermore, the results of studies conducted on diverse racial, age, and obesity groups are not well-supported by existing evidence. Additionally, there is a paucity of studies examining the impact of dietary interventions on diverse racial, age, and obesity groups, including those with genetic syndromes. These gaps highlight the necessity for future studies to adopt more standardized methods, consider more confounding factors, and conduct more in-depth analyses of different populations to improve the reliability and generalizability of findings.

Future directions and challenges

The potential of dietary and lifestyle strategies in the prevention of EC is gradually gaining recognition. An assessment of the current state of endometrial cancer prevention strategies reveals several gaps. These include limitations in research populations, insufficient long-term effectiveness and sustainability of interventions, the impact of cultural and socioeconomic factors, inadequate population-specific targeted research, and insufficient technology integration and policy support. Adopting healthy eating habits and lifestyles can significantly lower the risk of developing this type of cancer. However, specific guidance on how to effectively implement these strategies, the content and duration of dietary interventions, and the individual needs of patients have not been thoroughly studied, making it challenging to create universally applicable prevention programs.[9] Cultural and socioeconomic factors play a crucial role in shaping diet and lifestyle choices, which can impact the effectiveness of preventive measures.[66] Variations in cultural backgrounds may lead to differing perceptions and acceptance of healthy diets, highlighting the need for future research to focus on cultural adaptation to ensure that dietary and lifestyle interventions are both widely accepted and effectively implemented. Meanwhile, there is a notable gap in studies targeting specific populations; most existing research concentrates on the general population without delving into high-risk groups. On the technological front, the integration of digital health apps and wearable devices can play a key role in monitoring and promoting healthy lifestyles. These technologies have the potential to offer personalized health advice, assisting users in managing their diet and exercise more effectively, which may help reduce the risk of EC.[20] Additionally, support at the policy level is essential; targeted public health initiatives are necessary to enhance education about healthy diets and lifestyles, thereby increasing public awareness of the risks associated with EC and the importance of prevention. At the same time, the government and relevant organizations should promote further research and establish a collaborative framework that brings together experts from nutrition, public health, and gynecologic oncology. This multidisciplinary approach aims to identify the most effective practices and strategies for implementing dietary and lifestyle interventions, thereby providing a stronger scientific basis for the prevention of EC.[94] Future research should focus on large-scale cohort studies and genomic analyses to identify specific populations that would benefit most from targeted prevention strategies. In conclusion, while dietary and lifestyle modifications show promise for EC prevention, a shift from a one-size-fits-all approach to a personalized and diversified model is necessary. This includes identifying high-risk populations, developing measurable biomarkers, and integrating multiple disciplines to create comprehensive intervention systems. Addressing these challenges through rigorous scientific research and collaborative efforts will provide a more effective and sustainable solution for reducing EC incidence and improving public health.

Conclusions

Preventing EC remains complex and multifaceted, with lingering uncertainties in both research and clinical practice. The existing literature indicates that dietary and lifestyle interventions can significantly lower EC risk, but their effectiveness varies based on individual differences such as genetic predispositions, metabolic phenotypes, and cultural backgrounds. This review presents several key findings supported by the data. First, adherence to specific dietary patterns, like the Mediterranean diet, is associated with reduced EC risk due to the high intake of fruits, vegetables, whole grains, and healthy fats with anti-inflammatory and antioxidant properties. Second, regular moderate physical activity lowers EC risk through improved insulin sensitivity and reduced chronic inflammation. Third, the role of specific nutrients, such as long-chain omega-3 polyunsaturated fatty acids, remains controversial, with some studies indicating a protective effect, while others suggest potential risks, emphasizing the importance of considering the

broader dietary context. The review also highlights the paradoxical nature of lifestyle interventions, with low-intensity approaches often being more effective than high-intensity ones, and the impact of lifestyle modifications often overshadowed by genetic factors, particularly in LS individuals.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

Study design (YL, XZ), search performance (HA), data analysis (XZ, YL). All authors contributed to the editorial revision of the manuscript, read and approved the final version, and agreed to be fully accountable for all aspects of the work.

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