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Review Article

# Aspirin use and endometrial cancer risk and survival☆

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## HIGHLIGHTS

- Aspirin has been shown to have chemo-preventive effects on colorectal cancer.
- Aspirin can suppress platelet activation.
- Aspirin can indirectly inhibit prostaglandin $E_2$, an obesity-related inflammatory marker.
- Aspirin may improve the survival of women with endometrial adenocarcinoma.
- Effects of aspirin on endometrial cancer risk and survival is conflicting.

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## ABSTRACT

The role of acetylsalicylic acid (aspirin) as a chemo-preventive and adjuvant therapeutic agent for cancers is generating attention. Mounting evidence indicates that aspirin reduces the incidence and mortality of certain obesity-related cancers, particularly colorectal cancer. In endometrial cancer, previous studies examining the effect of aspirin remain inconsistent as to the reduction in the risk of endometrial cancer. While some evidence indicates protective effects in obese women, other studies have showed a potential deleterious effect of these medications on endometrial cancer outcomes. However, exposure measurement across studies has been inconsistent in recording dose, duration, and frequency of use; thus making comparisons difficult. In this article, we review the evidence for the association between endometrial cancer and obesity, the pharmacological differences between regular- and low-dose aspirin, as well as the potential anti-tumor mechanism of aspirin, supporting a possible therapeutic effect on endometrial cancer. A proposed mechanism behind decreased cancer mortality in endometrial cancer may be a result of inhibition of metastasis *via* platelet inactivation and possible prostaglandin $E_2$ suppression by aspirin. Additionally, aspirin use in particular may have a secondary benefit for obesity-related comorbidities including cardiovascular disease in women with endometrial cancer. Although aspirin-related bleeding needs to be considered as a possible adverse effect, the benefits of aspirin therapy may exceed the potential risk in women with endometrial cancer. The current evidence reviewed herein has resulted in conflicting findings regarding the potential effect on endometrial cancer outcomes, thus indicating that future studies in this area are needed to resolve the effects of aspirin on endometrial cancer survival, particularly to identify specific populations that might benefit from aspirin use.


**Contents**



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## 1. Introduction

Aspirin in its medicinal form has been used for its analgesic and anti-inflammatory properties for over a century [1]. Following elucidation of the anti-platelet effects of aspirin, the beneficial effects of low-dose aspirin for the primary and secondary prevention of cardio-vascular disease (CVD) have been established [2]. Recently, the United States Preventive Services Task Force (USPSTF) recommended "initiating low-dose aspirin use for the primary prevention of CVD and colorectal cancer in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years" [3]. While there is extensive evidence supporting the long-term use of aspirin for colorectal cancer prevention [4,5], evidence is building for decreasing overall risk and risk of metastasis in other malignancies such as esophageal and stomach cancer [4–7].

It is important to note that there are few studies focusing specifically on endometrial cancer, and caution should be taken in extrapolating results from other solid tumor types with varying histology to an individual disease. As such, the objective of this paper is to review current mechanistic and clinical evidence surrounding the effects of aspirin use on endometrial cancer risk and outcomes.

Endometrial cancer continues to be the most common gynecologic malignancy in the United States, with >61,000 newly diagnosed cases projected in 2017 [8]. Although the mortality rate in endometrial cancer patients is generally low, the survival rate for obese patients or those with metastatic or recurrent disease is significantly lower [9,10]. Established risk factors of endometrial cancer include obesity, unopposed estrogen therapy, tamoxifen use, nulliparity, polycystic ovarian syndrome, Lynch syndrome, early menarche, late menopause, and insulin resistance [9,11].

Over the last three decades, endometrial cancer has been commonly classified into two pathogenic types, although a lack of consensus for assigning these histotypes and the increasing ability to define tumor genotype is leading to a more precise molecular classification system [12]. Type I tumors are more common, generally arise in the setting of hyperestrogenism, are composed of low-grade endometrioid carcinoma, and carry an excellent prognosis [13]. Type II tumors, without clearly defined risk factors, are mainly represented by serous and clear cell carcinomas with an overall poor prognosis [12,14]. Endometrial cancer and colorectal cancer have many features in common, including risk factors, histopathologic progression from pre-cancerous lesion to carcinoma, as well as certain genetic mutations and microsatellite instability events [12,15]. These similarities lead to the hypothesis that some colorectal cancer findings, such as risk reduction with the use of aspirin, might be applicable to endometrial cancer.

## 2. Obesity, inflammation, and endometrial cancer

Obesity, the abnormal or excessive accumulation of body fat, is defined epidemiologically as a body mass index (BMI) of ≥30 among adults, and is an important risk factor for many chronic diseases, including type II diabetes, CVD, several cancers, and premature mortality [16]. Adipose tissue is a complex endocrine organ that secretes a variety of both anti- and pro-inflammatory cytokines classified as adipokines, which contribute to a state of chronic systemic inflammation [11]. Chronic inflammation associated with obesity has been known to be a major factor contributing to progression of many cancers [11]. In this proposed mechanism, obesity stimulates inflammatory pathways that promote tumor development, mainly by release of pro-inflammatory cytokines. These inflammatory cytokines then enhance angiogenesis, induce cell proliferation, suppress the immune system, and generate reactive oxygen species leading to DNA damage [17].

Obesity is also a well-established endometrial cancer risk factor. Incidence rates of endometrial cancer have steadily increased in the past two decades in parallel with the pandemic increase in the proportion of obesity in the United States [18]. Across all cancer sites, increased BMI and obesity is most strongly associated with endometrial cancer incidence and mortality [9–11,18].

The association between BMI and endometrial cancer is more prominent for type I endometrial cancer than type II endometrial cancer [14,19]. Traditionally, unopposed estrogen has been thought to be the primary oncogenic mechanism for the development of type I endometrial cancer in obese women [11]. Adipose tissue contains the aromatase enzyme, which peripherally converts circulating androgens, primarily androstenedione, into excess estrogen. This causes continued stimulation of the endometrium, resulting in endometrial hyperplasia, which can subsequently progress to invasive cancer. Aromatase expression in the intra-tumoral stroma, further contributes to intra-tumoral estrogen biosynthesis in endometrial carcinoma [20]. Interleukin-6 (IL-6) production is stimulated by 17β-estradiol in endometrial cancer cells and induces aromatase expression in intra-tumoral stromal cells, promoting further $E_2$ synthesis. This positive feedback loop further stimulates tumor cells.

Recent studies have elucidated that chronic inflammation related to obesity can be an important alternative mechanism of endometrial oncogenesis (Fig. 1) [21,22]. Inflammation contributes to the development of endometrial cancer in conjunction with estrogen exposure. Elevated serum levels of tumor necrosis factor-alpha (TNF-α), IL-6, and C-reactive protein (CRP) are associated with inflammation, and CRP in particular has been consistently associated with a statistically increased risk of endometrial cancer [22,23]. Chronic systemic inflammation associated with obesity augments the development of insulin resistance and chronic hyper-insulinemia, independent risk factors for the development of endometrial cancer [11]. The activation of pro-inflammatory pathways induced by TNF-α, over-expressed in adipose tissue, leads to a state of insulin resistance. The direct association between estrogen receptors and cell surface receptors, including insulin-like growth factor 1 receptor (IGFR-1) and epidermal growth factor receptor (EGFR), induces activation of many signaling pathways including the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway that promotes breast cancer cell growth and tumor progression [24]. The PI3K/AKT/mTOR pathway is known to be over-activated in a large fraction of endometrial cancers, due to loss of the tumor suppressor gene phosphatase and tensin homolog (PTEN). PTEN inactivation or loss is observed in >40% of type I endometrial