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Review article

# Hormone replacement therapy and the risk of endometrial cancer: A systematic review

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ABSTRACT

*Background:* In 1975, estrogen only was found to be associated with an increased risk of endometrial cancer. In November 2015, NICE guidelines on hormone therapy were published that did not take this risk into account.
*Aim:* This systematic literature review assesses the safety of estrogen plus progestin therapy according to the risk of endometrial cancer, while considering both regimen and type of progestin.
*Methods:* PubMed, EMBASE and the Cochrane Library were searched, resulting in the identification of 527 published articles on menopausal women with intact uteri treated with estrogen only, estrogen plus progestin or tibolone for a minimum of one year. Risk of endometrial cancer was compared to placebo or never users and measured as relative risk, hazard or odds ratio.
*Results:* 28 studies were included. The observational literature found an increased risk among users of estrogen alone. Continuous combined therapy showed a lower risk than sequential combined therapy. The newer marketed micronized progesterone increased the risk notably, also when administered continuously. In most studies, tibolone was associated with an increased risk.
*Conclusion:* Use of unopposed estrogen, tibolone and sequential combined therapy increases the risk of endometrial cancer. Continuous combined therapy seems risk free, but possibly not when micronized progesterone is used.



**Contents**



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## 1. Introduction

The median age at menopause in Europe and North America ranges from 50.1 to 52.8 years [1]. Menopausal symptoms comprise vasomotor symptoms, declining bone mass, vaginal dryness, insomnia and mood disturbances [2]. The mean duration is four years but in about 10% of women, they may continue for up till 12 years [3]. Menopausal hormone therapy is recommended as the most effective treatment for vasomotor symptoms [4]. Options are unopposed estrogen, combined therapy (estrogen and progestogen) or tibolone.

Unopposed estrogen ranges in potency; lowest in endogenic estriol over conjugated estrogen and 17β-estradiol to exogenic ethynyl estradiol in oral contraceptives as the strongest.

Progestogens can be classified as natural (the endogenous progesterone) or synthetic (progestins). Progestins can be further divided into those structured as progesterone (such as MPA, cyproterone acetate and dydrogesterone) and those structured as testosterone (such as norethindrone, levonorgestrel, norgestimate and gestodene) [5].

17β-estradiol acts through epithelial proliferation and primes the endometrium for the secretory state induced by progestogens. The latter causes cell differentiation, inhibits growth and converts 17β-estradiol to the less potent estrone by increasing enzymatic activity. Progestogens are considered an inhibitor of carcinogenesis and an endometrial tumor suppressor [5,6]. Unopposed estrogen increases the risk of endometrial hyperplasia [2] and risk of endometrial cancer is directly associated with circulating estrogen and androgen levels [7]. Endometrial hyperplasia is characterized by proliferation of endometrial glands. Incidence is estimated to 142/100,000 [8]. Hyperplasia without atypia has a risk of progression to endometrial cancer of less than 5% over 20 years, and the majority will progress spontaneously [9]. In Denmark, incident endometrial cancer is 769/year which corresponds to 364/100,000 women per year, or 4.2% of all female cancers [10].

Recently, in November 2015, new NICE guidelines on caretaking of menopause were published [11]. Data on hormone therapy (HT) were comprehensive but did not cover the risk of endometrial cancer. In this review we assess the risk of endometrial cancer among postmenopausal women treated with estrogen only, combined therapy or tibolone, by using both observational evidence as well as randomized studies.

## 2. Methods

This review follows the PRISMA 2009 guidelines.

### 2.1. Eligibility criteria

Women with an intact uterus being treated with systemic hormone therapy for menopausal symptoms. Participants were excluded if carrier of BRCA1 and 2 genes or if history of current or prior gynecological cancers, breast cancer, hysterectomy or hormonal therapy within one month prior to the beginning of the study.

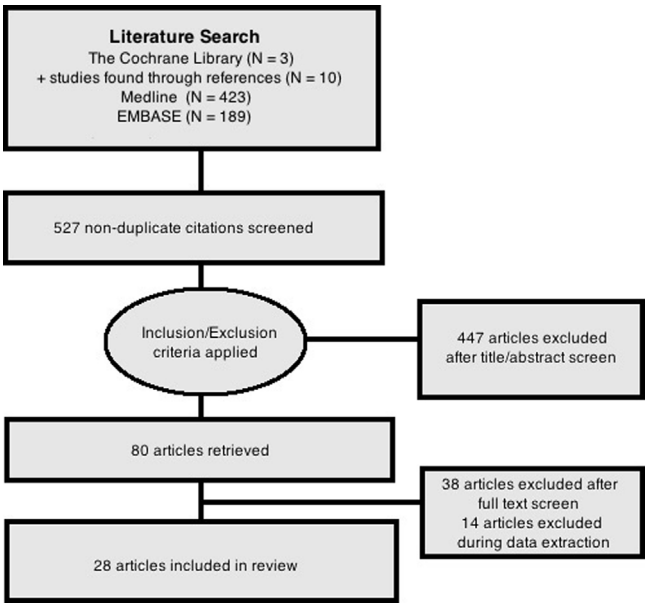


**Fig. 1.** Study selection flow chart.

Studies on any combination of unopposed estrogen, continuous and sequential combined estrogen plus progestin, tibolone compared with placebo or never-users were included. SERM and antiestrogens were not considered. Due to the different risk profiles, studies with no distinction between unopposed estrogen and combined estrogen plus progestin therapy were excluded. Only oral regimens and treatment lasting at least a year were considered in this review. Outcome was risk of endometrial cancer, measured as relative risk, odds or hazard ratio. Case-control studies were excluded. No restrictions were made on the length of follow-up.

All Cochrane relevant reviews as well as all randomized controlled trials (RCTs) published hereafter and all observational studies were included. Studies in English, French, Spanish or the Scandinavian languages were considered. Unpublished literature was not achieved.

### 2.2. Information sources and search strategy

The Cochrane Library was sought for reviews on hormone therapy and risk of endometrial cancer, browsing all studies subclassified under 'Menopause' in the gynecological section and reading analyses for relevant abstracts. Studies were chosen from