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Postmenopausal Hormone Therapy and the Risk for Uterine Cancers

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ABSTRACT

Large differences exist between countries in the context and use of postmenopausal hormone therapies. Differences also exist in genes, diet and lifestyle, which all affect the risk for cancers. I studied the effects of different estrogen-progestagen therapies (EPT) for the risk of endometrial and cervical cancer as well as uterine sarcoma in nationwide studies on postmenopausal Finnish women.

A cohort of all Finnish women (> 50 years of age) who had used EPT for at least 6 months since 1994 was collected from the national Medical Reimbursement Register and followed for uterine cancers with the aid of the Finnish Cancer Registry. The risks were compared to those of the same age background population in the three cohort studies. The follow-up for the endometrial cohort study ended in 2006 and encountered a total of 1,364 endometrial cancer cases out of a total of 224,015 women with EPT. The follow-up was continued until the end of 2008 in the other cohort studies and accumulated 243,857 women with EPT of which 192 women showed cervical precancerous lesions, 97 women cervical cancers and 76 women uterine sarcomas (45 leiomyosarcomas, 24 stromal sarcomas and 7 other sarcomas).

To control some of the various confounding factors and to assess, in addition to EPT, also the impact of tibolone, another study using a case-control study model was conducted. In total 7,261 women with endometrial cancer and 19,490 controls were compared in regard to the use of EPT or tibolone in 1995-2007. Hysterectomized women were excluded from the controls based on data from the Hospital Inpatient Register of the National Institute of Health and Welfare. Results were adjusted for parity, age at first delivery and hospital district, but not for body mass index, diabetes mellitus or socioeconomic status.

In the cohort study, the incidence of endometrial cancer was increased among sequential EPT users after 5 years of use (standardized incidence ratio (SIR) 1.69; 95% confidence interval (CI) 1.43-1.96) when progestagen was added monthly and the risk doubled to 3.76 (2.90-4.79) when progestagen was added at 3-month intervals. In the case-control study, sequential EPT showed increased risk only after 10 years of use (odds ratio (OR) 1.38; 1.15-1.66) but long-cycle sequential EPT associated with increased risk after 5 years of use (1.63; 1.12-2.38). The use of tibolone

showed no effect on endometrial cancer risk, but the number of cases (n = 19) was small. In contrast, the use of continuous combined EPT users was accompanied with a reduced risk for endometrial cancer from 3 years onwards (SIR 0.24; 0.06-0.60). Similar risk reductions for endometrial cancer were seen also in women using continuous combined EPT or an estradiol plus levonorgestrel releasing intrauterine system in the case-control study; the odds rations were 0.57 (0.37-0.88) and 0.16 (0.37-0.68), respectively.

In the cohort study, endometrial cancers of women using monthly sequential EPT tended to be diagnosed more often in a localized stage than endometrial cancers in general. The most common oral progestagens as parts of EPT in Finland (norethisterone acetate, medroxyprogesterone acetate and dydrogesterone) showed no significant differences in the endometrial effects. Transdermal and oral routes of administration showed similar risks for monthly sequential EPT regimen including estradiol and norethisterone acetate.

The incidence of cervical precancerous lesions in all EPT users did not differ from that in the background population, but the risk for squamous cell carcinoma was decreased (SIR 0.41; 0.28-0.58) and that of adenocarcinoma was increased (1.31; 1.01-1.67). When the use of EPT exceeded 5 years, the risk for squamous cell carcinoma showed a trend towards a further decrease 0.34 (0.16-0.65), and the risk of adenocarcinoma showed a trend towards an increase 1.83 (1.24-2.59).

The risk for uterine sarcomas was not affected by the exposure to EPT for less than 5 years. Uses of EPT for 5-10 and 10+ years associated with an increased risk for uterine sarcomas (SIR 2.02; 1.36-2.91 and 3.01; 1.30-5.93); risks were highest for leiomyosarcoma. The mode of EPT did not affect these risks significantly.

In conclusion, the use of postmenopausal EPT is one determinant for the occurrence of uterine cancers. Continuous combined regimens decrease and sequential regimens increase the risk for endometrial cancer; these data support earlier findings. The following new observations were made; oral and transdermal routes of administration or various types of progestagens do not modify these effects. A consistent decrease in the incidence of squamous cervical malignancies was seen in EPT users. In contrast, the incidence of cervical adenocarcinoma was increased. The risk for uterine sarcomas is increased if EPT has been used for longer times. These data are of importance for the potential users of EPT and for physicians prescribing such regimens.

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