

Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976–2004

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Endometrial cancer is a disease primarily driven by cumulative exposure to estrogen unopposed by progesterone. Reproductive factors associated with changes in endogenous hormone levels and use of exogenous hormones such as postmenopausal hormones influence the risk of disease. The authors used the Nurses' Health Study, comprised of 121,700 nurses, to assess the above associations. Over 28 years of follow-up, 778 adenocarcinoma cases were diagnosed and 1,850,078 person-years were accumulated. Cox proportional hazards models were used to estimate relative risks (RR) and 95% confidence intervals (CI). A late age at menarche decreased the risk independent of body mass index (BMI) (P -trend = 0.02). A late age at menopause increased cancer risk (P -trend = 0.0003). An advanced age at last birth reduced the risk (P -trend < 0.0001), however, an inverse association with age at first birth and parity diminished after adjustment for age at last birth. Compared with never-users, an increased risk was observed among long-term (≥ 5 years) users of both estrogen (E) (RR = 7.67, 95% CI: 5.57, 10.57) and combined estrogen plus progesterone (E+P) (RR = 1.52, 95% CI: 1.03, 2.23). Normal-weight (BMI < 25) women had the highest risk following E or E+P use (P -interaction-E = 0.0008, P -interaction-E+P = 0.02). The findings from this study underscore the importance of hormonal mechanisms in endometrial carcinogenesis.

Endometrial cancer is the most common gynecologic malignancy and the 4th most common type of cancer in women. Around 40,000 cases are diagnosed annually in the United States at an average age of 62 years.¹ The key components in endometrial cancer, a hormone-associated cancer, include estrogen and progesterone. The accepted etiological hypothesis, known as the unopposed estrogen hypothesis, explains that exposure of the endometrium to estrogen without concurrent exposure to progesterone stimulates endometrial cell proliferation, increasing the likelihood of genetic errors and malignant transformation.^{2,3} Progesterone opposes the estrogen effect by down-regulating estrogen receptors and promoting endometrial cell differentiation.³ An imbalance in these 2 hormones may be caused by excessive estrogen or a deficiency in progesterone.

Key words: adenocarcinoma, endometrial neoplasms, hormone replacement therapy, reproductive history

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Reproductive factors are likely risk factors for endometrial cancer because they are linked to endogenous hormone levels. Menarche, menopause and pregnancy are accompanied by major changes in endogenous hormone levels. Since 1988, at least 5 prospective cohort studies^{4–10} and at least 9 case-control studies (nested case-control,¹¹ population-based^{12–15} and hospital-based^{16–20}) reported on reproductive factors and endometrial cancer risk. Most of the studies agree that early age at menarche and a late age at menopause increase risk.^{7,8,10,13,14,20} However, among studies that describe an inverse association with age at menarche not all controlled for body mass index (BMI),^{7,8,10} which is a strong risk factor for endometrial cancer and a determinant of age at menarche. Nulliparity has been consistently associated with an increased risk, and a decrease in risk with increasing number of births has been observed in almost all studies.^{4,5,7,8,11–13,15,16,18} The role of timing of birth is less clear. Results are largely inconsistent on age at first birth as a possible risk factor, and recent studies report on a decreased risk associated with late age at last birth.^{6,7,11,16,17,19} To our knowledge, no studies have presented results examining the number of births controlling for age at last birth.

Studies on exogenous hormone use, specifically postmenopausal hormone use (PMH), provide more direct evidence of support for the unopposed estrogen hypothesis and highlight the importance of duration of exposure. Estrogen hormone use was initially prescribed to help ameliorate menopausal