Title: Estrogen Exposure Across the Transition to Menopause

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Abstract

The risk of morbidity and mortality from reproductive-related cancers increases post-menopausally, and risk for some reproductive cancers is associated with lifetime exposure to estrogen. We hypothesize that estrogen exposure during the peri-menopause may be a key factor influencing post-menopausal cancer risk. In a study of reproductive aging we examine total and unopposed estrogen levels across the peri-menopause, and compare them to pre-menopausal (before the peri-menopause) and post-menopausal levels.

U.S. participants (n=156, 25-58 years) collected daily urines for 6 months in each of 5 consecutive years. Exposure to total and unopposed estrogen was estimated using urinary estrogen (E) and progesterone (P). The ratio of E to P and the mitotic estrogen threshold are used as indicators of unopposed estrogen, and area under the curve is used as an indicator of total estrogen exposure. Linear mixed effects models are used to test the hypothesis that estrogen exposure, particularly unopposed estrogen, is elevated during the menopausal transition.

Extended Abstract

Background

It has become increasingly clear in recent years that there is a dose-response relationship between estrogen exposure across the lifespan and the risk of reproductive cancers, particularly of the endometrium, breast and ovary. These studies, coupled with epidemiologic data indicating that the age incidence of estrogen-related cancers increases disproportionately in the early postmenopausal years, suggest that the estrogen secretion patterns of the peri-menopausal years, when bleeding and hormonal patterns become disordered, may be an important source of risk. Detailed characterization of the estrogen

dynamics of the peri-menopausal years is thus an important step toward enhancing our understanding of estrogen dynamics and reproductive cancers in the postmenopausal years. We therefore monitored physiological levels of total and unopposed estrogen longitudinally across the transition to menopause in a large sample of women.

The transition to menopause is associated with increased variability in menstrual cycle length, and estrogen (E) and progesterone (P) patterns, when compared to the cyclical patterns of the prime reproductive years (Prior 1998, Klein and Soules 1998). In particular, previous cross-sectional and limited longitudinal studies (small sample sizes or short durations of observation) have observed unusually high levels of estrogen (Santoro et al 1996), increased frequency of anovulation (low P) (Vollman 1977), prolonged periods of elevated estrogen in older and peri-menopausal women (Santoro et al 1996, Prior 1998), and declining estrogen levels across the transition to menopause **(**Burger et al 1995). These seemingly conflicting reports of declining E with periods of unusual or prolonged elevation and an increase in unopposed E with reduced ovulation do not resolve whether women are exposed, overall, to more or less unopposed E, or to more or less overall E, across the transition to menopause when compared to unopposed and total E across the normal cycle and hormone patterns of the pre-menopausal years.

This is of concern because of the well documented association between high dose unopposed exogenous E and endometrial and other reproductive cancers (Hale et al. 2002). Only one study has explicitly characterized the degree of unopposed estrogen exposure in pre-menopausal and peri-menopausal women, using a ratio of estrogen to progesterone (Metcalf and Mackenzie 1985). Thirty peri-menopausal women were monitored once per week for 124 cycles of 18-260 days duration, and 66 pre-menopausal women once per week during 147 cycles of 22-36 days duration. Metcalf and colleagues reported that the percentage of time spent at high levels of E with reduced P exposure was significantly higher in the peri-menopausal than pre-menopausal women. They also reported that unusually long cycles (> 50 days) were common in peri-menopausal women and moreoever, tended to be associated with prolonged episodes of unopposed estrogen excretion. Although Metcalf and colleagues followed several women for multiple cycles, they examined each subject at only one reproductive stage (either peri-menopausal or pre-menopausal).

Estrogens stimulate mitosis in the endometrium and breast, and with this increase in cell division comes an increase in the likelihood of some reproductive cancers. Key and Pike (Key and Pike 1988) hypothesize that maximal mitotic activity in the endometrium is reached at relatively low levels of estrogen, but is stopped completely with sufficient progesterone exposure, mainly through the down-regulation of estrogen receptors in the layers of the endometrium where most cell proliferation occurs. If this is true, then progesterone may be the main modulator of cancer risk in pre-menopausal women who are likely to have estrogen levels sufficient to cause maximal mitotic activity in the endometrium throughout the menstrual cycle. The reverse is true in post-menopausal women, in whom estrogen secretion that accompanies episodes of follicular development is likely to be the main determinant of cell proliferation, as progesterone levels are expected to be constantly low. Progesterone may also affect risk of endometrial cancer through its control of the sloughing of the lining of the endometrium, which may eliminate abnormal cells before they become malignant. It is unclear exactly how much of the endometrium is lost during menstruation, and therefore whether normal menstruation results in elimination of any abnormal cells that may appear during the proliferative phase. However, studies of the use of sequential estrogen-progestin hormone replacement therapy suggest that varying the duration of progesterone use by even a few days can dramatically affect risk of endometrial cancer, perhaps because less progesterone exposure causes incomplete elimination of unhealthy cells (Pike & Ross, 2000). The predictions based on these studies are that poor luteal phases and anovulation will be highly significant determinants of endometrial cancer risk for cycling women, while frequency and duration of episodes of estrogen exposure not resulting in ovulation will determine risk in women after menopause (Key and Pike 1988). This work has not considered the peri-menopausal years.

The relationship between estrogens and breast cancer are less clear. Breast cancer risk seems to increase with the duration of a woman's life spent exposed to the endogenous sex hormones, all of which seem to increase breast cancer risk (Group 2002). However, studies of breast cancer risk associated with exogenous hormone use have not shown uniform agreement with this result, with some finding an increase in risk when estrogen and progesterone are taken together and no increase in risk with estrogen-only treatment. Ovarian estrogen secretion across the transition to menopause has been characterized in cross-sectional and limited longitudinal studies. Together, these studies have identified increased variability in estrogen secretion patterns across the transition when compared to the more regular ovarian cycle patterns exhibited during the prime reproductive years. The additional patterns suggested in these studies include: 1) long cycle segments of very low estrogen secretion (Harlow paper); 2) unopposed estrogen secretion associated with anovulatory cycles; and 3) prolonged episodes of high unopposed estrogen in very long cycles (Metcalf and Mackenzie 1985; Santoro et al; Shideler et al, Hee et al). Such patterns have particular relevance to the risk of endometrial cancer, as they may result in long periods of cell proliferation followed by no elimination or incomplete elimination of potentially abnormal cells. Despite the contributions of these studies, to the best of our knowledge, no studies have attempted to rigorously quantify total estrogen exposure across the menopausal transition in a sufficient sized sample.

Methods

Participants, recruited from the Tremin Research Program on Women's Health (n=156, 25-58 years), collected daily urine specimens for six months in each of five consecutive years and recorded menstrual bleeds for all months of each year. Specimens were assayed for estrone-3-glucuronide (E1G) and pregnanediol-3-glucuronide (PDG), urinary metabolites of estradiol and progesterone. Linear mixed-effects models were used to estimate exposure to total and unopposed estrogen across age and reproductive stage. Reproductive stage (regularly cycling, slightly irregular cycles, highly irregular cycles, postmenopausal) was estimated for each woman using menstrual cycle length variance. The ratio of E1G to PDG (a measure of total unopposed estrogen), an estimate of the mitotic estrogen threshold (MET) (a measure of unopposed estrogen only within the threshold), and area under the curve (AUC) (a measure of total estrogen) were used as indicators of different aspects of estrogen exposure. The mitotic threshold is the amount of estrogen necessary to cause mitotic endometrial changes and is the relevant unopposed estrogen measure for endometrial cancer. Linear mixed effects models are used to test the hypothesis that estrogen exposure, particularly unopposed estrogen, is elevated during the transition to menopause.

Results

One hundred fifty-six women ranging from 26 to 58 years of age at the start of the study participated in the study. Fifty-three women participated for the full 30 months (five 6-month study intervals) of the study and the average length of participation was 21 months (Ferrell et al 2005).

Analyses are only complete for the ratio of E1G to PDG. Controlling for the effects of age, BMI and censored cycles, the ratio of E1G to PDG increases in a dose response fashion as women move from regularly cycling to irregular cycling; after menopause the ratio is similar to that seen in normally cycling women. This effect is significantly modified by age, with PDG levels tending to be higher in older peri-menopausal women (>50 years), compared to younger (<50 years) peri-menopausal women. These results indicate that overall unopposed estrogen significantly increases across the transition to menopause. If the results for AUC and MET follow a similar trend, the findings will have important implications for the well-known increase in post-menopausal estrogen-related cancer risk as well as for clinical hormone therapy management; for example, women who spend a longer time in the transition may be at higher risk for reproductive cancers.