Emerging Common Strategies to Reduce Breast and Endometrial Cancer Risk

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**Abstract**

Breast cancer and endometrial cancer share several risk factors, including age, obesity and higher endogenous estrogen levels. As a result, these two cancers may be amenable to common risk reduction strategies. This possibility was evaluated in studies undertaken in the Women's Health Initiative (WHI) cohort and in the Kaiser Permanente Southern California (KPSC) integrated health plan. In the WHI Observational Study, intentional weight loss was associated with a significant reduction in endometrial cancer risk [hazard ratio (HR) 0.60, 95% confidence interval (CI) 0.42–0.86]. In the KPSC cohort of women with breast cancer, as might be expected given the known risk profile of tamoxifen, aromatase inhibitor use was associated with significantly lower endometrial cancer risk compared to tamoxifen use (HR 0.52, 95% CI 0.31–0.87). Compared to the no endocrine therapy group, aromatase inhibitor users had a trend towards fewer endometrial cancers (HR 0.71, 95% CI 0.37–1.35). As the aromatase inhibitors exemestane and anastrozole have been demonstrated to reduce breast cancer incidence in full scale primary prevention trials, findings from the studies outlined in this review suggest two potential strategies for reducing both breast cancer and endometrial cancer risk, especially in overweight and obese women who are most likely to develop these diseases.

**INTRODUCTION**

In the United States (US), breast cancer is the most common malignancy and the second most common cause of cancer death [1]. Endometrial cancer is the most common gynecologic cancer and the fourth most common cancer in women. In contrast to breast cancer, endometrial cancer does not have an established screening program for early detection; the disease is associated with a 15 to 20% three year mortality rate. Breast cancer and endometrial cancer share several risk factors, including age, obesity and higher endogenous estrogen levels. As such, these two common cancers may be amenable to shared risk reduction strategies. To begin evaluation of such a hypothesis, a series of investigations were undertaken in two population-based cohorts: the Women's Health Initiative (WHI) cohort and the Kaiser Permanente Southern California (KPSC) integrated health plan [2,3].

**STUDY POPULATIONS**

The WHI Clinical Trials were initially designed to evaluate the effects of hormone therapy on chronic disease in healthy postmenopausal women. Women were recruited at 40 centers in the United States from 1993 to 1998. Two hormone therapy trials were conducted: one compared combined estrogen and progestin to placebo in women with intact uteri, and the other compared estrogen alone to placebo in women who had undergone hysterectomy [4]. The primary end points for efficacy and safety were coronary heart disease and invasive breast cancer, respectively. In the estrogen plus progestin trial, 16,608 women aged 50 to 79 years with intact uteri, no history of invasive cancer within 10 years, and expected survival of at least 3 years were randomized to daily conjugated equine estrogens (CEE) 0.625 mg plus medroxyprogesterone acetate (MPA) 2.5 mg versus placebo. Endometrial biopsies were required at baseline. In the estrogen-alone trial, 10,739 women who had undergone hysterectomy were randomized to CEE 0.625 mg alone versus placebo.

The WHI Observational Study (OS) enrolled an additional 93,676 postmenopausal women who were either ineligible or not interested in participating in the clinical trials, or who were directly invited to participate in the OS [5]. This large cohort of women was diverse in terms of race/ethnicity and age and was prospectively followed to determine the natural history and risk factors for health conditions such as cancer, cardiovascular disease, and fractures.

The KPSC integrated health plan has over 4.2 million members in the Southern California region with 14 community-based hospitals and over 100 outpatient clinics. The integrated electronic medical record facilitates access to demographic information and health outcomes. Computerized pharmacy data provides exposure information. Incident breast and endometrial cancers are available from the KPSC National Cancer Institute

SEER-affiliated Cancer Registry. An ongoing breast cancer survivor cohort now includes over 25,000 women with invasive breast cancer diagnosed between 2004 and 2015. In the KPSC setting, outcomes in the breast cancer cohort can be compared to an age-matched cohort of women who are cancer free at study entry.

The above key study populations, as well as associated findings related to endometrial cancer risk, are described in Table 1. These findings can be compared to the results of full-scale, randomized placebo-controlled primary breast cancer prevention trials evaluating aromatase inhibitor use, which will be further described. The current report outlines common strategies for reduction of both endometrial and breast cancer risk.

**INFLUENCE OF WEIGHT LOSS ON RISK OF BREAST AND ENDOMETRIAL CANCER**

Obesity is associated with an increased risk of postmenopausal breast cancer [6,7] and endometrial cancer [8], as well as poorer survival after breast cancer diagnosis [9,10]. Approximately one third of women in the US are obese [11]. Thus, obesity is a common and modifiable factor which could influence both breast cancer and endometrial cancer incidence and outcome. Some studies suggest that bariatric surgery, which commonly results in substantial weight loss, is associated with a lower risk of endometrial cancer [12,13] and breast cancer [14], providing general proof of principle. However, the question remains unanswered as to whether moderate weight loss achievable in the clinic for overweight or obese postmenopausal women decreases the risk of these cancers.

Observational studies have yielded mixed findings on the association of weight loss in postmenopausal women and breast cancer risk. Weight loss was not associated with breast cancer risk in some studies [15,16], while in others, weight loss was associated with lower risk [17,18]. In an analysis of 67,042 postmenopausal women participating in the WHI clinical trials, no association between weight loss and subsequent breast cancer incidence was found [19]. Similarly, observational studies have been unable to delineate an association between adult weight loss and lower endometrial cancer risk [3]. We hypothesized that differences in intentional versus unintentional weight loss may have contributed to these inconsistencies [20].

The WHI dataset included in formation about weight changes over time as well as the intentionality of the weight changes, thus providing an important opportunity to evaluate the association of weight loss intentionality with endometrial cancer and breast cancer incidence among overweight and obese postmenopausal women. In the WHI Observational Study, anthropometric measures were obtained at baseline and year 3. At year 3, participants were asked: “In the past 2 years, did you gain or lose 5 or more pounds?” and “Was the change intentional or unintentional?”

Luo and colleagues [3], examined the incidence of endometrial cancer after the WHI Observational Study year 3 visit and found a significant association between voluntary weight loss and subsequent lower endometrial cancer incidence over 11.4 years of follow-up. Women who had weight loss ≥ 5% from baseline to the year 3 visit had a lower risk of developing endometrial cancer than women with stable weight (HR 0.71, 95% CI 0.54-0.95). When this group was examined for intentionality of weight loss, the difference in endometrial cancer incidence was significant for those with intentional weight loss (HR 0.60, 95% CI 0.42-0.86) but not for those with unintentional weight loss (HR 0.94, 95% CI 0.62-1.41). Currently, similar studies evaluating weight loss intentionality and breast cancer incidence in postmenopausal women are underway in the same WHI population, with the hope of establishing a common risk reduction approach for both endometrial and breast cancer.

**Table 1: Key studies of endometrial cancer risk.**

<table>
<thead>
<tr>
<th>Population</th>
<th>Design</th>
<th>Subjects</th>
<th>Outcome of interest</th>
<th>Key findings related to endometrial cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser Permanente Southern California Chlebowski et al. Cancer 2015 [2]</td>
<td>Observational cohort</td>
<td>Cohort of postmenopausal women with ER and/or PR positive breast cancer, stage 0-IV, from an integrated health practice plan</td>
<td>Endometrial cancer incidence, by type of adjuvant endocrine therapy used (AI, tamoxifen, both [switching], or neither)</td>
<td>- Tamoxifen only compared to no endocrine therapy: HR 1.36, 95% CI 0.84-2.22, P=0.22</td>
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<td>- AI only compared to no endocrine therapy: HR 0.71, 95% CI 0.37-1.35, P=0.30</td>
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<td>- AI only compared to tamoxifen only: HR 0.52, 95% CI 0.31-0.87, P=0.01</td>
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<tr>
<td>Women’s Health Initiative Randomized Clinical Trial Chlebowski et al. JNCI 2015 [39]</td>
<td>Randomized, double blind, placebo controlled trial</td>
<td>Postmenopausal women from the Women’s Health Initiative, randomized to estrogen + progestin or placebo for a median of 5.6 years</td>
<td>Endometrial cancer incidence, by estrogen + progestin use</td>
<td>- Endometrial cancer yearly incidence, 0.06% vs 0.10%; HR 0.65, 95% CI 0.48 to 0.89, P = 0.007</td>
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<tr>
<td>Women’s Health Initiative Observational Study Luo et al. JCO 2017 [3]</td>
<td>Observational cohort</td>
<td>Cohort of postmenopausal women from the Women’s Health Initiative Observational Study</td>
<td>Endometrial cancer incidence, by change in weight over a 3 year period (stable, weight gain, or weight loss)</td>
<td>- Weight gain (≥5% body weight): HR 1.12, 95% CI 0.92-1.38</td>
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<td>- Weight loss (≥5% body weight): HR 0.71, 95% CI 0.54-0.95</td>
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tamoxifen and raloxifene for breast cancer chemoprevention has been well described [21]. However, uptake of this intervention strategy has been limited in clinical practice due to concern regarding increased endometrial cancer risk [22].

The effectiveness of aromatase inhibitors in reducing breast cancer incidence has been established in two large, randomized, placebo-controlled clinical trials. MAP.3 was an international trial of postmenopausal women deemed to be at elevated risk for breast cancer who were randomized to the aromatase inhibitor exemestane (n = 2285) or placebo (n = 2275) for 5 years. The primary endpoint was invasive breast cancer. At a median follow-up of 35 months, exemestane reduced the risk of invasive breast cancer by 65% (11 cases in the exemestane group versus 32 in the placebo group, HR 0.35, 95% CI 0.18-0.70, p=0.002) [23]. IBIS-II was an international trial of postmenopausal women deemed to be at elevated risk for breast cancer who were randomized to the aromatase inhibitor anastrozole (n = 1920) or placebo (n = 1944) for 5 years. The primary endpoint was any breast cancer, invasive or non-invasive. At a median follow-up of 5 years, anastrozole reduced the risk of invasive and non-invasive breast cancer by 53% (40 cases in the anastrozole group versus 85 in the placebo group, HR 0.47, 95% CI 0.32-0.68, p<0.0001). The number of women needed to be treated to prevent one case was 36 [24].

In the aromatase inhibitor prevention trials, more adverse events occurred in the aromatase inhibitor groups compared with the placebo groups. Statistically significant differences were seen for endocrine-related adverse events (vasomotor symptoms), some nausea and not infrequent joint and muscle pain. Of interest, the musculoskeletal symptoms occurred with much less frequency in these prevention trials than in adjuvant trials in which the same agents were used in women with early stage breast cancer [23,24]. There were no significant differences in the incidence of serious adverse events including cardiovascular events, fractures, other cancers, or treatment-related deaths [23,24]. Studies on the influence of aromatase inhibitors on cardiovascular disease and lipid profile have yielded conflicting results, and further investigation is needed [25].

Similar to breast cancer [26], endometrial cancer has been associated with elevated endogenous estrogen levels in observational studies [26,27]. As aromatase inhibitors decrease endogenous estrogen, they could potentially decrease endometrial cancer risk. In this regard, limited studies have found clinical benefit for aromatase inhibitors in advanced endometrial carcinoma [28].

Chlebowski and colleagues [2], examined this hypothesis in a cohort of 17,064 postmenopausal women with hormone receptor positive breast cancer from the KPSC community-based integrated health practice. Women with stage 0-IV estrogen and/or progesterone receptor positive breast cancer diagnosed from 1991 to 2010 were identified and followed for incident endometrial cancer. Use of adjuvant tamoxifen alone, aromatase inhibitor alone, both (“switchers” were defined as using at least 6 months of tamoxifen and at 6 least months of aromatase inhibitor), or neither was tracked using pharmacy data. Endometrial cancer incidence was significantly lower with aromatase inhibitor compared to tamoxifen use (HR 0.52, 95% CI 0.31-0.87, P = 0.01).

Also, compared to the no endocrine therapy group, aromatase inhibitor users had a trend towards fewer endometrial cancers (HR 0.71, 95% CI 0.37–1.35, P=0.30). Furthermore, the group of “switchers” had a trend toward lower endometrial cancer incidence compared to the tamoxifen only group (HR 0.67, 95% CI 0.42–1.06, P=0.08)); this association approached statistical significance when only women with good medication adherence (defined as medication possession ratio >80%) were examined (HR 0.59, 95% CI 0.34-1.01, P=0.055) [2]. While further study is needed, the findings are suggestive of a potential role for aromatase inhibitors in endometrial cancer risk reduction in addition to breast cancer risk reduction.

**INFLUENCE OF MENOPAUSAL HORMONE THERAPY ON RISK OF BREAST AND ENDOMETRIAL CANCER**

The effects of menopausal hormone therapy on breast cancer risk in postmenopausal women are complex, with variation in risk/benefit balance depending on time from hormone therapy use [29-31]. However, the association between unopposed estrogen use and increased endometrial cancer risk has been known for over 40 years [32,33]. The addition of progesterin to exogenous estrogen mitigates endometrial cancer risk [34-36]. Although recent cohort studies reported significantly lower endometrial cancer risk in estrogen plus progestin users [35], current guidelines do not describe combined hormone therapy as reducing endometrial cancer incidence [37,38].

The influence of combined estrogen plus progestin on endometrial cancer was addressed in the WHI randomized trial described previously in this review. Over 13.2 years of median cumulative follow-up, combined estrogen plus progestin use significantly decreased endometrial cancer incidence (P=0.007) [39]. However, the potential increase in breast cancer risk precludes its acceptance as a strategy for endometrial cancer chemoprevention [30,31]. While detailed information about the risks and benefits of estrogen plus progestin use in any clinical setting is beyond the scope of the current report, long term follow-up of the WHI randomized clinical trials indicate no overall benefit for chronic disease risk reduction [4].

**CONCLUSIONS**

In the WHI observational cohort, intentional short-term weight loss was associated with substantial reduction in endometrial cancer risk. Parallel studies regarding weight loss intentionality and breast cancer risk are underway in the WHI cohort. Two large phase 3 trials have established aromatase inhibitors as lowering breast cancer risk. In addition, in a large community-based cohort of breast cancer patients, a trend toward lower endometrial cancer risk was seen with use of aromatase inhibitors. Taken together, findings from these studies support consideration of two potential strategies for reducing both breast cancer and endometrial cancer risk, namely weight loss/maintenance and aromatase inhibitor use. A potential target population would be overweight and obese women who are at increased risk of these two cancers. Additional studies are needed to explore this concept with potential impact on two major women’s cancers.
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CONTRIBUTORS

KP wrote the initial draft of the report. Authors KP and RTC had full access to the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. KP, RTC, JL, RH, and GLA provided critical review of the manuscript for important intellectual content. RTC, JL, RH, and GLA collected the data and obtained study funding.

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ADDITIONAL INFORMATION

A full list of all the investigators who have contributed to Women’s Health Initiative science appears at: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.p

REFERENCES


