Update of HRT for menopause

JAMES F. DEVANNEY, MD
UROLOGIST

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My past highlights

- University of CT Medical school 1990
- University of Virginia Urology 1995
- Women’s Health Initiative (WHI) 2002
- Age Management conferences 2008-present
- Cenegenics Fellowship 2012
Menopause

- What is it?

  Defined by the absence of menstruation for 12 months or low serum levels of Estrogen, progesterone and testosterone.

  Average age 54 (95% occur between 45 and 57)
What do you mean by hot!
Menopause

What are the symptoms of menopause?

- Headaches and hot flashes
- Teeth loosen and gums recede
- Risk of cardiovascular disease
- Backaches
- Body and pubic hair becomes thicker and darker
- Bones lose mass and become more fragile
- Vaginal dryness, itching, and shrinking
- Hair becomes thinner and loses luster
- Breasts droop and flatten
- Nipples become smaller and flatten
- Skin and mucous membranes become drier, skin develops a rougher texture
- Abdomen loses some muscle tone
- Stress or urge incontinence
Menopause

- What has been done for women?
  - Nothing
  - Mono therapy with Estrogen
  - Combination therapy with Estrogen and Progesterone
  - Symptom therapy- antidepressants and sleep aides
Study Highlights

- **First HRT = Estrogen replacement (Premarin)**

  - Unfortunately unopposed Estrogen increased risk of uterine cancer
  - Addition of Progestin (medroxyprogesterone acetate) eliminated risk

**Great news for Wyeth pharmaceutical company.**
Historical hormone therapy

How woman have been treated has made some feel like they are on a roller coaster!
Women Health Initiative Study - 2002

- 10,739 woman who had hysterectomy – Estrogen alone
- 16,608 with uterus randomized to E+P or placebo
Increased risk for:

1. Breast cancer (26% increased occurrence)

38 cases in E+P vs 30 in placebo population 10,000!
Increased risk for:

2. Stroke (41% increase)

29 cases E+P vs 21 placebo 10,000
Increased risk for:

3. Heart Attack (29%)

37 cases E+ P vs 30 in placebo group
WHI Conclusions

- Increased risk of breast cancer seen as unacceptable
- Previous cardiac protection not realized

Stop HRT
What have we learned since?

- 12 years have lapsed
- Major critiques have come forward
  1. Average age of woman in study 67. (13 years after start of menopause)
  2. Estrogen alone arm reduced breast cancer occurrence
  3. Type of progesterone used matters!
Progestin = Progesterone

- No
Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort

Agnès Fournier¹, Franco Berrino², Elio Riboli², Valérie Avenel¹ and Françoise Clavel-Chapelon¹*

¹Equipe E3N, Institut National de la Santé et de la Recherche Médicale (INSERM), Villejuif, France
²Unit of Nutrition and Cancer, International Agency for Research on Cancer (IARC-WHO), Lyon, France
³Department of Preventive and Predictive Medicine, Istituto Nazionale Tumori, Milan, Italy

Most epidemiological studies have shown an increase in breast cancer risk related to hormone replacement therapy (HRT) use. A recent large cohort study showed effects of similar magnitude for different types of progestogens and for different routes of administration of estrogens evaluated. Further investigation of these issues is of importance. We assessed the risk of breast cancer associated with HRT use in 54,548 postmenopausal women who had never taken any HRT 1 year before entering the E3N-EPIC cohort study (mean age at inclusion: 52.8 years; 948 primary invasive breast cancers were diagnosed during follow-up (mean duration: 5.8 years). Data were analyzed using multivariate Cox proportional hazards models. In this cohort where the mean duration of HRT use was 2.8 years, an increased risk in HRT users compared to nonusers was found (relative risk (RR) 1.2 [95% confidence interval 1.1–1.4]). The RR was 1.1 [0.8–1.6] for estrogens used alone and 1.3 [1.1–1.5] when used in combination with oral progestogens. The risk was significantly greater (p < 0.001) with HRT containing synthetic progestins than with HRT containing micronized progesterone, the RRs being 1.4 [1.2–1.7] and 0.9 [0.7–1.2], respectively. When combined with synthetic progestins, both oral and transdermal/percutaneous estrogens use were associated with a significantly increased risk; for transdermal/percutaneous estrogens, this was the case even when exposure was less than 2 years. Our results suggest that, when combined with synthetic progestins, even short-term use of estrogens may increase breast cancer risk. Micronized progesterone may be preferred to synthetic progestins in short-term HRT. This finding needs further investigation.

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Material and methods

E3N is a French prospective study investigating cancer risk factors in 98,997 women born between 1925 and 1950. All women belong to the MGEN, a health insurance scheme primarily covering teachers. Part of the E3N cohort (i.e., women who replied to a dietary questionnaire) is also included in the European Prospective Investigation into Cancer and Nutrition (EPIC). Since June 1990, after having given informed consent, participants have been asked at approximately 24-month intervals to complete self-administered questionnaires including a variety of lifestyle characteristics. For each questionnaire, up to 2 reminders were sent to nonrespondents. Information on lifetime use of hormonal treatments was first recorded in the January 1992 questionnaire. In
Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study

Agnes Fournier · Franco Berrino · Françoise Clavel-Chapelon

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Abstract Large numbers of hormone replacement therapies (HRTs) are available for the treatment of menopausal symptoms. It is still unclear whether some are more deleterious than others regarding breast cancer risk. The goal of this study was to assess and compare the association between different HRTs and breast cancer risk, using data from the French E3N cohort study. Invasive breast cancer cases were identified through biennial self-administered questionnaires completed from 1990 to 2002. During follow-up (mean duration 8.1 postmenopausal years), 2,254 cases of invasive breast cancer occurred among 80,377 postmenopausal women. Compared with HRT never use, use of estrogen alone was associated with a significant 1.29-fold increased risk (95% confidence interval 1.02–1.60). The association of estrogen–progestagen combinations with breast cancer risk varied significantly according to the type of progestagen: the relative risk was 1.00 (0.83–1.22) for estrogen-progesterone, 1.16 (0.94–1.43) for estrogen-dydrogesterone, and 1.69 (1.50–1.91) for estrogen combined with other progestagens. This latter category involves progestins with different physiologic activities (androgenic, nonandrogenic, antiandrogenic), but their associations with breast cancer risk did not differ significantly from one another. This study found no evidence of an association with risk according to the route of estrogen administration (oral or transdermal/percutaneous). These findings suggest that the choice of the progestagen component in combined HRT is of importance regarding breast cancer risk; it could be preferable to use progesterone or dydrogesterone.

Keywords Breast cancer · Cohort · Dydrogesterone · Estrogen · Hormone replacement therapy · Menopause · Progestagens · Progesterone

Introduction

Estrogen-progestagen postmenopausal hormone replacement therapy (HRT) has been classified as carcinogenic to humans with respect to breast cancer, on the basis of both observational studies and randomized controlled trials [1]. However, small structural changes in progestagens may considerably alter their effects [2, 3]. Until now, most studies have evaluated estrogen associated with medroxyprogesterone acetate or 19-nortestosterone derivatives [4, 5], but other combined estrogen-progestagen therapies are used around the world and it is still unclear whether some are more hazardous than others. The relationship between estrogen-only therapy and breast cancer risk is also the subject of intense debate: unopposed estrogen use was associated with a decreased risk of breast cancer in the Women’s Health Initiative (WHI) trial [6], but not in some observational studies [7–14].

Millions of women are still using HRTs, as estrogen remains the most effective treatment to alleviate menopausal symptoms [15]. It is therefore crucial to
**Table 4** Relative risks for invasive breast cancer by type of HRT and recency of use, compared with HRT never-use

<table>
<thead>
<tr>
<th></th>
<th>Last use [0–2] years previously</th>
<th>Last use [2–5] years previously</th>
<th>Last use ≥5 years previously</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/PY  (^a)</td>
<td>Relative risk (^b) (95% CI)</td>
<td>Cases/PY  (^a)</td>
</tr>
<tr>
<td>Estrogen alone</td>
<td>47/13,834</td>
<td>1.22 (0.90–1.65)</td>
<td>8/1,312</td>
</tr>
<tr>
<td>Estrogen combined with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone</td>
<td>115/35,804</td>
<td>1.03 (0.84–1.26)</td>
<td>9/1,369</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>96/26,910</td>
<td>1.22 (0.98–1.52)</td>
<td>3/1,219</td>
</tr>
<tr>
<td>Other progestagens</td>
<td>461/90,478</td>
<td>1.75 (1.54–1.99)</td>
<td>13/3,720</td>
</tr>
</tbody>
</table>

\(^a\) PY = person-years. For each HRT type, the numbers of cases and person-years in the different recency of use strata do not add up to the totals (cf. Table 3) because of missing information

\(^b\) Adjusted for the same covariates as in Table 2
The Kronos Early Estrogen Prevention Study

- Average age of woman – 52 as compared to 67.
- Doses of Estrogen and Progesterone different

- 3 groups
  1. Oral Premarin + micronized progesterone
  2. Transdermal Estradiol (E-2) + micronized progesterone
  3. Placebo
Highlights of KEEPS

- Both HT groups had reduced symptoms of menopause
  - Hot flashes
  - Night sweats,
  - Improved bone density
  - Improved sexual performance

- In Contrast to WHI study NO increase blood pressure observed

- Oral estrogen associated with
  - Increased HDL
  - Decreased LDL

- Transdermal Estrogen
  - Improved glucose levels
  - Improved insulin sensitivity

- NO increased risk of breast cancer detected!
SPECIAL FEATURE

The North American Menopause Society Recommendations for Clinical Care of Midlife Women

Jan L. Shifren, MD, NCMP, Margery L.S. Gass, MD, NCMP
for the NAMS Recommendations for Clinical Care of Midlife Women Working Group

In celebration of the 25th anniversary of The North American Menopause Society (NAMS), the Society has compiled a set of key points and clinical recommendations for the care of midlife women. NAMS has always been a premier source of information about menopause for both healthcare providers and midlife women. At this special time in the history of the Society, we wished to provide a succinct guide to improve the understanding and management of women’s health at this critical stage of life. In addition to covering the key topics of vasomotor symptoms, osteoporosis, and vulvovaginal health, this guide includes information and recommendations for care on more than 50 important topics, including sexual function, cognition, cardiovascular health, thyroid disease, and cancers. Additional sections review basic physiology, counseling issues, screening tests, and complementary and alternative medicine.

The basis for these key points and clinical recommendations is the NAMS premier textbook, *Menopause Practice: A Clinician’s Guide*. Published originally in 2000 and updated approximately every three years to remain current, this clinical practice textbook provides in-depth coverage of all areas of interest to clinicians who care for women at midlife. Each topic is written by an expert in the field, including internationally recognized gynecologists, internists, medical and reproductive endocrinologists, cardiologists, neurologists, psychiatrists, psychologists, dermatologists, oncologists, and counselors. Relevant research is described in detail, and each topic is accompanied by an extensive list of references. NAMS Recommendations for the Clinical Care of Midlife Women, published in this edition of *Menopause*, will be freely available on the NAMS website to promote high-quality care for women throughout the world. These recommendations provide a brief overview of each topic presented in the textbook. Clinicians who wish to learn more about a particular subject or intervention by an Editorial Panel, with final review and approval by the 2013-2014 NAMS Board of Trustees. The Editorial Panel was comprised of experts in midlife women’s health from a wide range of specialties who devoted significant time and effort to ensuring the accuracy and relevance of each key point and clinical recommendation. Every clinical recommendation is accompanied by a level of evidence, and the strength of each recommendation is based on the highest level of evidence found in the data.

Recommendations are provided and graded according to the following categories:
- Level I—based on good and consistent scientific evidence.
- Level II—based on limited or inconsistent scientific evidence.
- Level III—based primarily on consensus and expert opinion.

We hope these evidence-based recommendations will be a valuable resource for clinicians and further the mission of NAMS, at its 25th anniversary, to promote the health and quality of life of all women during midlife and beyond.

Jan L Shifren, MD, NCMP
President, NAMS
Editor-in-Chief, NAMS Recommendations for the Clinical Care of Midlife Women

Margery L.S. Gass, MD, NCMP
Executive Director, NAMS
Editor, NAMS Recommendations for the Clinical Care of Midlife Women

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**CHAPTER 1: MENOPAUSE**

Overview of menopause

Somatic, psychic, and hormone production
NAMS
Summary Recommendations

- Treat symptomatic menopausal women
- Use lowest does of Estrogen to control symptoms
- Did not recommend use of progesterone
- Did not recommend use of testosterone
- Did not recommend HRT for disease prevention BUT recognized emerging data favoring early replacement
<table>
<thead>
<tr>
<th>n</th>
<th>Duration</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td>12 weeks</td>
<td>↑ Desire, arousal and fantasies</td>
<td>[64]</td>
</tr>
<tr>
<td>40</td>
<td>10 weeks</td>
<td>↑ Masturbatory pleasure. No change in sexual behavior and arousal. Normal sexual function at baseline</td>
<td>[65]</td>
</tr>
<tr>
<td>34</td>
<td>12 months</td>
<td>↑ Bone density, sexual activity, pleasure, satisfaction and orgasm</td>
<td>[21]</td>
</tr>
<tr>
<td>66</td>
<td>24 months</td>
<td>↑ Bone density; ↓ HDL; ↓ TG</td>
<td>[66]</td>
</tr>
<tr>
<td>28</td>
<td>9 weeks</td>
<td>↑ Bone formation; ↓ TC; ↓ HDL</td>
<td>[67]</td>
</tr>
<tr>
<td>53</td>
<td>12 weeks</td>
<td>↓ BMI; ↑ sense of well being</td>
<td>[68]</td>
</tr>
<tr>
<td>75</td>
<td>12 weeks</td>
<td>↑ Sexual activity, pleasure, orgasm, fantasies and well being</td>
<td>[69]</td>
</tr>
<tr>
<td>36</td>
<td>16 weeks</td>
<td>↑ Sexual activity and pleasure, lean body mass and selective strength; ↓ fat mass</td>
<td>[70]</td>
</tr>
<tr>
<td>31</td>
<td>12 weeks x 2 crossover</td>
<td>↑ Well-being, mood and sexual function</td>
<td>[71]</td>
</tr>
<tr>
<td>218</td>
<td>16 weeks</td>
<td>↑ Sexual desire and responsiveness</td>
<td>[72]</td>
</tr>
<tr>
<td>107</td>
<td>8 weeks</td>
<td>↑ Sexual desire/interest</td>
<td>[73]</td>
</tr>
<tr>
<td>447</td>
<td>24 weeks</td>
<td>↑ Frequency of SSE and desire</td>
<td>[74]</td>
</tr>
<tr>
<td>533</td>
<td>24 weeks</td>
<td>↑ Frequency of SSE and desire</td>
<td>[75]</td>
</tr>
<tr>
<td>562</td>
<td>24 weeks</td>
<td>↑ Frequency of SSE and desire</td>
<td>[76]</td>
</tr>
<tr>
<td>549</td>
<td>24 weeks</td>
<td>↑ Frequency of SSE and desire; ↓ personal distress</td>
<td>[77]</td>
</tr>
<tr>
<td>77</td>
<td>24 weeks</td>
<td>↑ Sexual desire, arousal, orgasm, responsiveness and self-image; ↓ sexual concerns and distress</td>
<td>[78]</td>
</tr>
<tr>
<td>61</td>
<td>16 weeks</td>
<td>↑ Immediate and delayed visual and verbal memory, and simple concentration (unaffected by aromatase inhibition)</td>
<td>[79]</td>
</tr>
<tr>
<td>76</td>
<td>16 weeks</td>
<td>↑ Sexual satisfaction, well-being and mood (unaffected by aromatase inhibition)</td>
<td>[80]</td>
</tr>
<tr>
<td>36</td>
<td>12 weeks</td>
<td>↑ Sexual desire, frequency of sex, receptivity and initiation</td>
<td>[81]</td>
</tr>
<tr>
<td>814</td>
<td>52 weeks</td>
<td>↑ Desire, arousal, orgasm and self-image; ↓ distress (150- and 300-µg doses); ↑ SSE and ↑ hair (300-µg dose)</td>
<td>[54]</td>
</tr>
<tr>
<td>261</td>
<td>16 weeks</td>
<td>↑ SSE (90-µl dose)</td>
<td>[82]</td>
</tr>
<tr>
<td>28</td>
<td>52 weeks; four acute</td>
<td>↑ Sexual cues; ↑ genital response and subjective indices of sexual function with added PDE5</td>
<td>[83]</td>
</tr>
</tbody>
</table>