



Dr. Wulf H. Utian has served as Editor-in-Chief of *Menopause Management* since its inception in 1988. Arthur H. Bill Professor Emeritus of Reproductive Biology and Obstetrics and Gynecology at Case Western Reserve University, he is President of Rapid Medical Research, headquartered in Cleveland, and is Consultant in Women's Health to the Cleveland Clinic Foundation. He is a Fellow of both the Royal and American Colleges of Obstetricians and Gynecologists, a Fellow of the International College of Surgeons and a board-certified reproductive endocrinologist.

A pioneer in menopause research, Dr. Utian founded the world's first menopause clinic in Cape Town, South Africa, in 1966 and established the Cleveland Menopause Clinic in 1983.

Recipient of many research grants and awards, he is the author of more than 150 scientific publications and five books. He is the Honorary Past-President of the International Menopause Society and Honorary Founding President and Executive Director of The North American Menopause Society. He is also Chairman of the Council of Affiliated Menopause Societies (CAMS) of the International Menopause Society.

HRT and Cancer

Are estrogenic steroids carcinogenic? Attempts to answer this perplexing question are beginning to resemble those around the question, "When does life begin?"

The debate on this issue gathered steam at the end of 2000, when an advisory panel to the National Toxicology Program issued a press release stating that they had recommended that steroidal estrogens be listed as "known to be a human carcinogen" — rather than the previous designation of "reasonably anticipated to be a human carcinogen." NAMS released a response on its Web site (www.menopause.org) stating, *inter alia*, that ERT, although long known to substantially increase the risk of endometrial cancer, showed attenuation of this risk when combined with the appropriate progestogen therapy. The question of whether estrogens were causally related to breast cancer, or merely to growth promoters, was stated to be unresolved.

An annual report on carcinogens is federally mandated by the Public Health Services Act (Section 301[b]4). The National Toxicology Program (NTP) was established in 1978 by the Secretary of Health and Human Services and involves the National Institutes of Health, the Centers for Disease Control and Prevention, and the FDA. A final response to the recommendation of the advisory panel has not yet been issued.

Further reports have escalated the debate. For example, postmenopausal estrogen use for 10 or more years was said to be associated with an increased ovarian cancer risk that persisted up to 29 years after cessation of use.¹ While fraught with methodologic problems, the study in which these findings were put forth has raised the level of concern with regard to HRT and cancer.

On the plus side of the equation, an example relates to colon cancer. The second most common cancer in women in developed countries appears to be reduced in incidence for ever-use of HRT, as analyzed from 14 observational studies showing a relative risk of 0.8.²

The breast cancer issue remains unresolved but somewhat reassuring. It is generally conceded that HRT is associated with a slight increase in risk of breast cancer that is restricted to current and recent users; progestogens do not appear to diminish this risk, and might indeed be the factor for enhancing it.² Diagnosed cancers appear to be less aggressive than those in never-users, and no increase in mortality has been demonstrated.

None of the above really gets to the core issue of whether estrogens are carcinogens. The International Menopause Society convened a closed meeting of world experts in Pisa, Italy, during June 2001 to consider this quandary. Ultimately, deliberations centered on cause and effect. The details of the panel discussions are presented in this issue of *Menopause Management*. The conclusion reached was that sex steroids are not known to damage DNA directly; they can, nonetheless, stimulate or inhibit cell proliferation, and thus can modulate tumor progression and growth.

Ultimately, you and your patients will discuss this question. Hopefully, the material presented in this issue will be of some value to you for those discussions. The decision about whether to prescribe to a woman at risk for a specific cancer continues to be counterbalanced by the potential benefit anticipated for the specific indication being considered. If there is no clear reason to prescribe, then there is no justification to assume risk.

A handwritten signature in black ink that reads "Wulf H. Utian". The signature is written in a cursive, flowing style.

Wulf H. Utian, MD, PhD
 Executive Director and
 Honorary Founding President
 The North American Menopause Society

References

1. Rodriguez C, Patel AV, Calle EE, et al. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA* 2001;285:1460-5.
2. Clinical Synthesis Panel on HRT. Hormone replacement therapy. *Lancet* 1999;354:152-5.