Study Links HT With Higher Ovarian Cancer Risk

Critics fault the Million Women Study because the data on HT use are based entirely on patient recall.

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An additional 1,000 women may have died from ovarian cancer linked to hormone therapy during a 15-year period in the United Kingdom, according to results from an enormous, but controversial, epidemiologic study.

After 6.5 million woman-years of follow-up, investigators for the Million Women Study concluded that those taking HT were 20% more likely to develop and die from ovarian cancer than those who had never taken it, but that the risk for women who quit taking HT returned to baseline by 5 years (Lancet 2007 [Epub doi:10.1016/S0140-6736(07)60534-0]).

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Hormone therapy accounted for one extra case of ovarian cancer and one extra death per 2,500 users over a 5-year period, wrote Dr. Valerie Beral, lead author for the Million Women Study Collaboration. "If this association is causal, the use of HT since 1991 has resulted in roughly 1,300 extra cases of ovarian cancer and 1,000 extra deaths from the malignancy in the U.K.," the investigators wrote.

From 1991 to 2001, the study—the largest epidemiologic study of its kind—enrolled 1.3 million women aged 50-64 years. All had been invited to the National Health Service Breast Screening Programme and completed an initial survey about social, demographic, and lifestyle factors, including the use of HT. About 3 years after recruitment, the women received a second questionnaire to secure updated information on HT.

Other researchers have questioned the MWS results since its first publication in 2003, saying that its methodologic problems make its conclusions difficult to interpret or accept.

The MWS ovarian cancer analysis included 948,576 women: 474,682 had never used HT, 186,751 were past users, and 287,143 were current users. The subjects' mean age at last follow-up was 57 years; 56% had used oral contraceptives, and 20% were current smokers.

The women were followed for an average of 5 years to determine ovarian cancer incidence. During that time, 2,273 such cancers were reported to the national registry. Current users were 20% more likely than never-users to develop the cancer—a significant difference. There was no difference in incidence between never-users and past users.

Current users had been taking HT for an average of 8 years at the time of diagnosis, and incidence increased with the duration of HT. Women who had taken hormones for 10 or more years were at a 30% increased risk for disease, compared with never-users.

But the risk of developing ovarian cancer dropped rapidly after ceasing HT. Compared with women who had never used HT, the relative risk for ovarian cancer was 1.01 for women who had been off HT less than 5 years and 0.95 for those who were off HT 5 or more years.

There were no significant differences in the risks between HT preparations (different estrogenic and progestogenic components; oral or transdermal; or between preparations with progestagens). Likewise, the researchers wrote, there were no significant associations with any demographic factor. Adjusting for age, socioeconomic status, body mass index, physical activity, or alcohol and tobacco use did not alter the relative risk for current users by more than 2%.

HT users who had undergone hysterectomy did have a significantly increased risk, compared with those who had not, but the researchers said that was probably because they had been taking HT longer.

The women were followed for an average of 7 years to determine ovarian cancer mortality. During this time, 1,591 deaths were attributed to ovarian cancer. Women who were current users of HT at their last follow-up were 23% more likely to die from the disease than never-users. Past users were at no significantly increased risk of death.

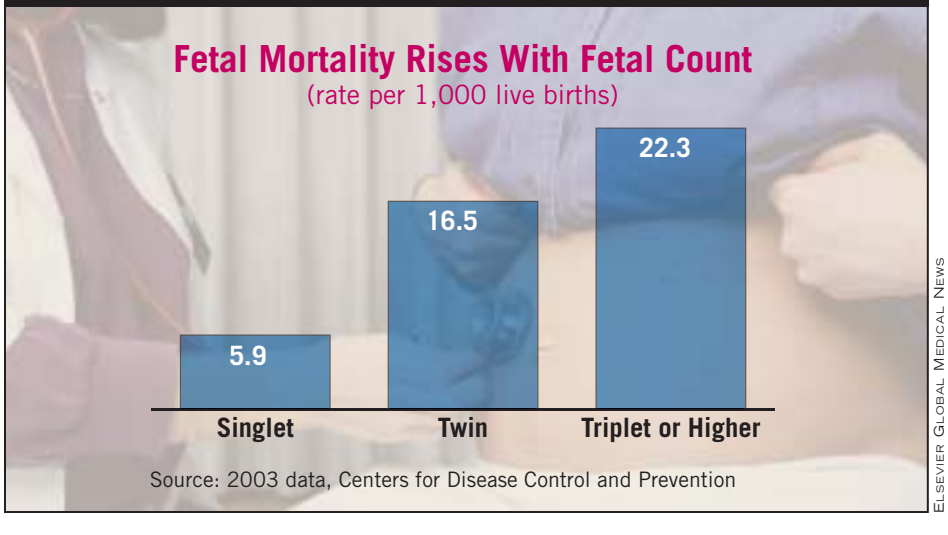
Again, there were no significant differences in risk after the researchers adjusted for demographic characteristics. There were also no significant differences in the risk of death between the different preparations of HT or the mode of administration.

The standardized ovarian cancer incidence rate was 2.2/1,000 women per 5 years among never-users and 2.6/1,000 women per 5 years in current users. The standardized mortality rate was 1.3 deaths/1,000 women per 5 years among never-users and 1.6/1,000 women per 5 years in current users.

But these numbers cannot be viewed in isolation, wrote the authors, whose study has previously examined the incidence of breast and endometrial cancers in these women. "Ovarian, endometrial, and breast cancer account for 39% of all cancers registered in women in the United Kingdom. The total incidence of these three cancers in the study population is 63% higher in current users of HT than in never-users. Thus, when ovarian, endometrial, and breast cancer are taken together, use of HT results in a material increase in the incidence of these common cancers."

Dr. Steve Narod, of the Women's College Research Institute, Toronto, agreed. "[The risk] might be thought of as small, but enormous numbers of women have been exposed," he wrote in an accompanying commentary" (Lancet 2007 [Epub doi:10.1016/S0140-6736(07)60535-2]). ■

DATA WATCH



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Study Controversial From the Start

There's no doubt that the Million Women Study has been directly responsible for the dramatic decrease in British and European hormone therapy prescriptions, experts say. But they also point out that criticism has dogged this enormous epidemiologic study every step of the way. Since 2003, critics have charged that a flawed methodology makes MWS' conclusions almost impossible to accept.

Critical response began with the first MWS publication in 2003. The Lancet published several letters questioning its methodology in the same issue that carried the breast cancer study (Lancet 2003;362:1330-1).

British epidemiologist Richard Farmer is one of several researchers who have repeatedly challenged the investigation's methodology. "Both [the breast cancer and endometrial cancer] studies have the same serious design flaws and there are important aspects of the published reports that are inconsistent," wrote Dr. Farmer, emeritus professor of epidemiology at the University of Surrey (England) (Climacteric 2005;8:210-3).

Dr. Farmer and his colleague, Dr. M. Whitehead reported in 2004 that the study's design flaws "render the results largely uninterpretable because built-in biases have affected risk estimates" (Endoc. 2004;24:187-93).

Nevertheless, the Million Women Study carried the same national and international impact as did the U.S. Women's Health Initiative. Immediately after the first MWS publication, Britain's drug regulatory agency, the Committee on Safety of Medicines, announced that the data confirmed an HT duration–dependent increase in the risk of breast cancer, and advised counseling patients of that risk.

MWS significantly influenced HT prescribing patterns in the United Kingdom and throughout Europe. In the Netherlands, for instance, the publication of WHI was followed by a modest decrease in prescribing of HT. But after publication of the initial MWS results, rates dropped precipitously (Br. J. Clin. Pharm. 2005;60:641-7).

The study's main flaw is that HT use is based entirely based on recall—a notoriously unreliable source of information, said Dr. James Fiorica, director of gynecologic oncology at Saraso-ta Memorial Hospital, Fla., and a member of the speakers' board at Wyeth Pharmaceuticals, which manufactures the HT drugs Prempro and Premarin.

"MWS was questionnaire based," he said in an interview. "This gives you no idea of compliance, or how long these women were really on hormones. It's easy to attribute cancer risk to a drug, but very hard to draw these conclusions based on a questionnaire."

Dr. Wulf Utian, executive director of the North American Menopause Society, said the MWS ovarian cancer data won't change any of the HT prescribing recommendations included in the group's recent position statement. "The Million Women Study data are absolutely riddled with methodological problems; most serious investigators are not certain how to interpret these data," Dr. Utian said in an interview. "The only conclusion we can draw from this study is that, clearly, we do not have all the answers. HT carries both potential benefit and potential risk, but in most instances, these absolute risks are rare."

Treatment decisions should be based on a women's individual risk profile, he said. "If a woman of low risk and high need is prescribed HT she has little to fear. On the other hand, a woman of high risk and weak indication for HT would be better off to concentrate on healthy living and other more appropriate remedies for her problem."