What is the clinical and economic return on taxpayers' $260M investment in the WHI?

145,000 more quality-adjusted life years and at least $23.1 billion. According to sensitivity analysis, the 95% confidence interval for the net economic return of the Women's Health Initiative (WHI) estrogen plus progestin trial was $23.1 to $51.2 billion. Beyond life years, base-case analysis also indicated 126,000 fewer breast cancers and 76,000 fewer cardiovascular disease cases occurred because of the WHI, though 263,000 more fractures occurred.

FAST TRACK

Medical expenditure savings from fewer EPT users and decreased breast cancer and CVD incidence amounted to $35.2 billion

Roth JA, Etzioni R, Waters TM, et al. Economic return from the Women's Health initiative estrogen plus progestin clinical trial: A modeling study. Ann Intern Med. 2014;160(9):549–602.

EXPERT COMMENTARY

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The WHI estrogen plus progestin (EPT) clinical trial, a $260 million venture, is among the most expensive projects ever undertaken by the National Institutes of Health. Following 2002 publication of its initial findings, use of EPT and estrogen alone (ET) hormone therapy (HT) among US women plummeted. Investigators, including WHI leadership, estimated the clinical and economic impact of this trial from a payer perspective.

Details of the study

For the years 2003 to 2012, the authors used a disease-simulation model to evaluate the effect of the WHI EPT trial on women aged 50 to 79 with an intact uterus (women who were combined-HT [cHT], or EPT, eligible). They compared outcomes between a "WHI scenario," in which the prevalence of cHT use was based on actual WHI findings, with a "no-WHI" scenario, in which pre-WHI trends in cHT use (from 1998 to 2002) were linearly extrapolated.

The simulation model predicted that 9.5 million women used cHT in the no-WHI scenario, 4.3 million more than actually used cHT in the WHI scenario. The authors estimated that, compared with the no-WHI scenario, 126,000, 76,000, and 80,000 fewer respective cases of breast cancer, cardiovascular disease (CVD), and venous thromboembolism occurred and that 263,000 and 15,000 more respective cases of fractures and colorectal cancer occurred among women as a result of the WHI.

Regarding economic outcomes, the authors estimated that the WHI resulted in $35.2 billion in direct medical expenditure savings—principally from fewer prescriptions for EPT and associated office visits ($26.2 billion), but also from decreased breast cancer incidence ($4.5 billion) and

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Dr. Kaunitz reports that he receives grant or research support from Bayer, Noven, Teva, and Trimel, and that he is a consultant to Actavis, Bayer, and Merck.

8.4 Pediatric Use
Safety and efficacy of Skyla have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal females under the age of 18 as for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use
Skyla has not been studied in women over age 65 and is not approved for use in this population.

8.6 Hepatic Impairment
No studies were conducted to evaluate the effect of hepatic disease on the disposition of LNG released from Skyla *[see Contraindications (4)]*.

8.7 Renal Impairment
No studies were conducted to evaluate the effect of renal disease on the disposition of LNG released from Skyla.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Patient Information)

- Counsel the patient that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases (STDs).
- Counsel the patient on the benefits, risks, and side effects of Skyla prior to insertion. Provide the Patient Information Booklet and give her the opportunity to read the information and discuss fully any questions she may have concerning Skyla as well as other methods of contraception. Advise the patient that the Full Prescribing Information is available to her upon request.
- Inform the patient about the risks of ectopic pregnancy, including the loss of fertility. Teach her to recognize and report to her healthcare provider promptly any symptoms of ectopic pregnancy.
- Inform the patient about the possibility of PID and that PID can cause tubal damage leading to ectopic pregnancy or infertility, or infrequently can necessitate hysterectomy, or cause death. Teach patients to recognize and report to their physician promptly any symptoms of pelvic inflammatory disease. These symptoms include development of menstrual disorders (prolonged or heavy bleeding), unusual vaginal discharge, abdominal or pelvic pain or tenderness, dyspareunia, chills, and fever.
- Counsel the patient that irregular or prolonged bleeding and spotting, and/or cramps may occur during the first few weeks after insertion. If her symptoms continue or are severe she should report them to her healthcare provider.
- Counsel the patient on how she can check that the threads still protrude from the cervix and caution her not to pull on the threads and displace Skyla. Inform her that there is no contraceptive protection if Skyla is displaced or expelled. *[See Warnings and Precautions (5.6, 5.7).]*
- Instruct the patient to contact her healthcare provider if she experiences any of the following:
  - A stroke or heart attack
  - Very severe or migraine headaches
  - Unexplained fever
  - Yellowing of the skin or whites of the eyes, as these may be signs of serious liver problems
  - Pregnancy or suspected pregnancy
  - Pelvic pain or pain during sex
  - HIV positive seroconversion in herself or her partner
  - Possible exposure to sexually transmitted infections (STIs)
  - Unusual vaginal discharge or genital sores
  - Severe vaginal bleeding or bleeding that lasts a long time, or if she misses a menstrual period
  - Inability to feel Skyla's threads
- Inform the patient that Skyla can be safely scanned with MRI only under specific conditions *[see Warnings and Precautions (5.11)]*. Instruct patients who will have an MRI to tell their doctor that they have Skyla. This information is included on the Follow-Up Reminder Card.
- Complete the Follow-up Reminder Card and give to the patient.

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Examining the
EVIDENCE

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

At first glance, the clinical and economic benefits of the WHI EPT trial appear enormous. However, the authors surprisingly failed to take into consideration relevant issues well known to women's health clinicians: lower use of systemic HT (both in women with an intact uterus and those posthysterectomy) has resulted in many more women suffering from bothersome vasomotor and sleep-related menopausal symptoms, with resultant impairment of quality of life.

In addition, the authors did not account for the major reduction in use of ET after the 2002 WHI findings in women who have had a hysterectomy; given that ET reduces the incidence of breast cancer and cardiovascular disease, declines in ET use have resulted in increased morbidity and mortality from these conditions.[1]

Finally, as the profound declines in use of systemic HT have not been accompanied by a substantive increase in the use of vaginal estrogen, we have an epidemic of symptomatic vulvovaginal atrophy, with attendant sexual dysfunction and impaired quality of life.

›› ANDREW M. KAUNITZ, MD

decreased CVD incidence ($2.2 billion), among other savings, which offset increases in expenditures for greater fracture incidence ($4.8 billion) and colorectal cancer ($1.0 billion).

In addition, the investigators reported a tremendous gain in quality of life years (145,000) in the WHI versus the no-WHI scenario, attributing the difference to the greater health-related quality-of-life effect associated with decreased breast cancer and CVD incidence in the WHI scenario.

Reference

1. Sarrel PM, Njike VY, Vinante V, Katz DL. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. Am J Public Health. 2013;103(9):1583–1588.