



Putting the WHI Study into Clinical Perspective

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Key Points

- The short-term risks of oral hormone therapy in 50- to 59-year-old women appear to be confined to venous thromboembolic events and gallbladder disease; heart disease and stroke do not appear to be increased.
- With use of combined therapy longer than 3 to 5 years, the risk of breast cancer increases. Mammographic abnormalities and breast biopsies increase with estrogen or combined hormone therapy.
- Most risks, as well as benefits, associated with hormone therapy disappear after 3 years of discontinuing therapy. An increase of all cancers (breast, lung, and colon) after stopping hormone therapy requires further study.

The results of the combined therapy arm of the Women's Health Initiative (WHI), first published 6 years ago, reverberated throughout the medical community as long-held beliefs regarding the benefits of postmenopausal hormone therapy for prevention of chronic diseases were shattered. The overall risks (heart attack, stroke, venous thromboembolic events [VTEs], and breast cancer) exceeded the overall benefits (reduced incidence of fracture and colon cancer). Since the original WHI publications, further analyses have shown that the risks and benefits vary depending upon the type of hormone therapy (estrogen alone versus estrogen plus progestin), the duration of hormone therapy, the age of the woman at the time of initiation of hormone therapy, and the



Unraveling the Complexities of Menopause Management

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years since menopause. The questions for practitioners and women alike are: 1) what are the risks for short-term use of hormone therapy for relief of vasomotor symptoms in the young, healthy, recently postmenopausal woman who presents for therapy, and 2) what are the risks, or benefits, after therapy is discontinued?

The risks of CHD and stroke do not appear to be increased with hormone therapy use in younger women. The short-term vascular risks for healthy women in their 50s seeking relief of vasomotor symptoms with hormone therapy are likely limited to approximately one episode of VTE per 1000 woman-years. The risk of breast cancer (0.5 per 1000 woman-years) increases after 3 to 5 years of combined therapy (no increased risk after 7 years of estrogen alone). However, both mammographic abnormalities and breast biopsies increase in women on hormone therapy. The risk of gallbladder disease increased overall by 2 to 3 cases per 1000 woman-years, but the risks were not stratified by age.

The health risks and benefits 3 years after stopping therapy in the combined arm of the WHI study were recently reported for the entire cohort without stratification by age. The risks of hormone therapy-associated vascular events (coronary heart disease, stroke, VTE) were no longer increased. Conversely, there was no fracture benefit 3 years after study completion. The risk of 'all cancer' was increased by 3 per 1000 woman-years of therapy at the end of the 3-year follow up. The cancers included breast, predominantly lung, and colon. Future elaboration of the cancer findings might help to identify women who require surveillance after discontinuing hormone therapy.



For a healthy 50-year-old woman today with severe menopausal symptoms, the benefits of hot flash relief, improvement in vaginal symptoms, and bone preservation with short-term hormone therapy likely exceed the small risks of VTE and gallbladder disease. The small increased risk of breast cancer after 3 to 5 years of use and the potential negative effect of hormone therapy on mammography and breast biopsies will have to be factored into each woman's personal decision about hormone therapy. Practitioners are currently encouraged to prescribe half the dose of hormones used in the WHI; whether the risks are reduced concordantly remains to be established. Whether other hormone therapy preparations or modes of delivery have a different risk/benefit profile merits further study.

Suggested Readings

Anderson GL, Chlebowski RT, Rossouw JE, et al. Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin. *Maturitas*. 2006;55:103-115.

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Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297:1465-1477.