

Will women be swayed by HRT's preventive benefits?

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Allegations that initial reports of a major women's health study exaggerated the risks of hormone replacement therapy (HRT) have reignited debate about use of the treatment, particularly shortly after menopause for the prevention of chronic disease.

"We've maybe gone too far to say HRT is only for your symptoms and we don't even talk about the preventive benefits," says Dr. Jennifer Blake, chief executive officer of the Society of Obstetricians and Gynaecologists of Canada (SOGC). "Should women not be aware of the full story before they make up their minds?"

Up until 2002, women routinely took HRT for symptoms of menopause, as well as to prevent osteoporosis and heart disease. But everything changed when the Women's Health Initiative (WHI) trial of estrogen plus progestin — the largest ever of HRT — linked the treatment to increases in the incidence of breast cancer and heart disease.

As *CMAJ* recently reported, an [initial results paper](#) and [press release](#) overstated the significance of these findings, when in fact, the risks were statistically insignificant. And although the study was designed to focus on women over age 60 and long past menopause, the results were generalized to younger women, who comprise the majority of HRT patients.

"Younger women, who had always been the appropriate candidates for HRT, were basically thrown under the bus," says Dr. Robert Langer, a WHI principal investigator. He claims study executives [played up the breast cancer angle](#) to court publicity. In the media frenzy that followed publication of the initial results, use of HRT plummeted by as much as 80%.

The fallout in North America and around the world has been "tragic," says Dr. Robert

Reid, author of the SOGC hormone therapy guidelines. "Millions of women were denied treatment that is safe and effective, and they've suffered for years."

Women who stopped HRT had a [55% greater risk of hip fracture](#), resulting in an estimated 43 000 fractures per years in the US alone. Another study estimates [18 601 to 91 610 American women died prematurely](#) between 2002 and 2012 as a result of avoiding estrogen therapy.

Medical societies are again recommending short-term HRT for women within 10 years of menopause. But Reid says "strong beliefs about risks are very resistant to change, even in the face of contrary evidence."

That's particularly true when it comes to the preventive benefits of HRT. Most

guidelines still acknowledge the value of HRT in preventing osteoporosis, but only some medical societies have issued [cautious statements](#) that there may be a "window of opportunity" in which the treatment prevents heart disease. Both American and Canadian task forces on preventive care recommend against preventive use of HRT.

"It's a very, very current area of controversy and ongoing discussion," says Blake.

But there is longstanding evidence that suggests the benefits of preventive use may outweigh the risks in some women. Observational studies over the past 50 years consistently link HRT with a 30%–50% reduction in heart disease and overall mortality in postmenopausal women. A



Experts now agree hormone therapy is safe for women within 10 years of menopause, but there's still an uphill battle to put old fears to rest.

major difference between these studies and the WHI estrogen-progestin trial was the participants' age. The observational studies looked at women aged 45 to 55 who started HRT near the onset of menopause, whereas the average age of participants in the estrogen-progestin trial was 63.

"If you had tried with the same population to test whether exercise was good for your heart, and you put 70-year-olds on a treadmill and cranked it up, some of them are going to have a heart attack because they've got a preexisting coronary artery disease," Reid says. "It's really not fair to extrapolate data from 60- and 70-year-olds to 50-year-olds."

A [reanalysis of the WHI data](#) in 2007 found that women who started estrogen plus progestin closer to menopause tended to have reduced heart disease risk. Another WHI trial of estrogen alone reported a [30%-45% reduction in heart attacks and other measures of heart disease](#) among participants aged 50–59, in line with earlier observational studies. That study also showed a 23% reduction in breast cancer, regardless of age. In a [2012 *Climacteric* article](#), American cardiologist

Dr. Howard Hodis concluded that these and other studies show that HRT confers the greatest protection against heart disease "when initiated in women before 60 years of age." The risks of the treatment were comparable to other common medications, such as aspirin and statins.

Langer says this evidence "hasn't really penetrated into clinical practice because the degree of fear around breast cancer so poisoned the climate." Fear has also distorted perception of the risk, he adds. Estrogen plus progestin increased breast cancer by less than one case per 1000 women, the World Health Organization threshold for a "rare" drug effect. But there was no increased risk when women took HRT for less than 5.6 years, and many women take hormones for shorter periods.

Dr. JoAnn Manson, another WHI investigator, argues that the risks and benefits of HRT are too individual and complex to support preventive use. She allows that "a case can be made" for using HRT to prevent osteoporosis, and guidelines still support that use. At this point, however, "it will be enough of an advance if HRT is used appropriately for management

of menopausal symptoms," she says. "There's no need to go overboard."

Reid says the biggest challenge ahead will be retraining physicians, particularly the "decade of graduates from medical school who have never prescribed HRT." He also hopes government will remove inaccurate black-box warnings on hormone products.

Others have called for an [independent inquiry](#) into the misinformation surrounding the WHI study.

Langer admits that he and other WHI investigators' efforts to correct misunderstanding in the "genteel scientific way" haven't worked. "We need to somehow find a way to get the message back out to the public that the supposed science that was sold to them 15 years ago was not correct."

Langer will deliver his account of the "sordid behind the scenes manipulation that got us to this point" to SOGC members in Ottawa on June 21, 2017.

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This is the second part of a two-part article on hormone replacement therapy. Part one, "Trial overstated HRT risk for younger women," was published May 1 at [cmaj.ca](#).