

# Hormone Therapy: Rigour and Responsibility in Knowledge Translation

**Robert L. Reid, MD, FRCSC**

Professor, Obstetrics and Gynaecology, Chair, Division of Reproductive Endocrinology and Infertility, Queen's University, Kingston ON

*Exposure to media coverage of women's health risks can itself be hazardous to one's health if those who create the news and those who cover it are not prepared to do a balanced, accurate, and informative job of presenting a given problem.*

Cristine Russell, Special Health Reporter for the *Washington Post*

In North America, the greatest number of women in history will reach the age of 50 in 2009, and it is therefore hardly surprising that menopause, osteoporosis, cancer, and hormone therapy have become such hot topics. Women's health has emerged as an area of great interest for contemporary consumers, fuelled by women's magazines, celebrity books, talk shows, and advocacy groups for breast cancer and the like.

Knowledge translation is emerging as a critical determinant of therapeutic choice in our increasingly consumer-driven health care system. Researchers and clinicians on the front line of discovery face the daunting task of generating enthusiasm for their findings while ensuring that these are presented truthfully, in context, and in a way that has meaning to a public that generally lacks the ability to understand the nuances of science. Compounding this challenge is the need for reporters to further distill this information into a short, often simplistic, summary in a matter of hours, leaving just enough time for an editor to develop the sensational headline that will draw readers away from the many other media options available to them.

In 2002, the first reports from the Women's Health Initiative (WHI) shook the medical world, as headlines around the world conveyed the unsettling news that the first large-scale randomized placebo-controlled trial of hormone therapy did not demonstrate a reduction in cardiovascular disease, but actually showed the opposite.<sup>1</sup> Subsequent headline news from the WHI suggested that hormone therapy increased the risk of heart attack, stroke, breast cancer, dementia, and incontinence, while affording no

improvement in health related quality of life—surely a rebuff to the prevailing opinion that hormone therapy could improve health, extend life, and afford a superior quality of life.

Both scientists and reporters bear responsibility for the accuracy of information conveyed to the public. Common errors that affect the validity of such reports include (1) the use of convenience samples for research, with extrapolation of the findings to other dissimilar groups, (2) description of benefits or risks as “relative risks” rather than “absolute” or “attributable risks,” (3) failure to put the benefits or risks into context by comparing the level of risk with the levels of other lifestyle or therapeutic choices that may afford the same benefits or confer the same risks, and (4) presentation of research findings to the public before they have undergone rigorous peer review for methodological or statistical shortcomings or faulty conclusions. Each of these problems has been evident as results of the WHI have been communicated to the public.

The first WHI publication was written and released without input from many of the study's co-investigators, and subsequent WHI publications were routinely released to the press by the publishers to garner as much sensational media coverage as possible. Unfortunately, follow-up publications with adjudicated reports and more in-depth analysis from the WHI suggesting that HT is a safe option for newly menopausal women have seen much less media play.

Many newspapers reported the original negative findings of the WHI as relative risks (e.g., a 29% increase in risk of heart attack in HT users), leaving some readers wondering whether this meant that 29 of every 100 users would succumb to cardiac disease. Media could have more effectively communicated the level of risk by reporting the attributable risk of 7/10 000 HT users per year (after central adjudication, this number fell to 6/10 000 and was no longer statistically significant<sup>2</sup>). The *New York Times*, trying to “one-up” the competition, went so far as to publish a table showing “number needed to treat/harm” for the WHI results.

Unfortunately, by pooling results from women in their fifties with results from women in their seventies, they calculated numbers that did little to inform an anxious public about the true risks and benefits of HT for a newly menopausal woman.<sup>3</sup>

To their credit, the WHI investigators have clearly shown the futility of starting hormone therapy late in life to prevent or delay cardiovascular disease or dementia. In this respect the WHI data were timely and important. For newly menopausal women with distressing vasomotor symptoms, however, the WHI publicity—together with other reports on breast cancer risk with HT—have fuelled a billion-dollar market for largely ineffective and unproven complementary and alternative therapies, as women desperately seek relief from these symptoms.

Much has been written about the WHI in the years since the first publication. The design has been criticized for the inclusion of large numbers of older women (two thirds of subjects were over age 60, with fully 21% in their seventies at enrolment), raising doubts about the validity of extrapolating the cardiovascular findings (and possibly the findings on cognition and dementia) to newly menopausal women seeking hormone therapy for relief of vasomotor symptoms. Responding to such criticisms, the WHI published a subgroup analysis in 2007 looking at coronary heart disease according to age and years since menopause.<sup>4</sup> They could demonstrate no increase in coronary artery disease when HT began within 10 years of menopause and, indeed, reported lower mortality (1/1000 hormone users per year) in this population of HT users.

Some of the WHI investigators have continued to argue that their original study findings prove that long-term hormone therapy will afford no cardiovascular benefit, yet the study was really not appropriately designed to address this question. The proper design, a randomized controlled trial of newly menopausal women, is probably impossible. Estimates suggest that it would require 128 000 women aged 55 to 59 who are willing to remain on HT or placebo for 10 years to detect a 10% reduction in coronary heart disease.<sup>5</sup> The logistics and costs for such a trial would be staggering.

A large body of observational data suggests that hormone therapy may be cardioprotective.<sup>6</sup> Additionally, premature loss of ovarian function appears to increase the risk for premature cardiovascular disease.<sup>7</sup> A recent report from the WHI found that women who had bilateral oophorectomy could halve their risk of developing coronary artery calcium if they took HT.<sup>7</sup> The conclusion that the findings are “consistent with the thesis that the estrogen deficiency associated with bilateral oophorectomy is related to an increased burden of calcified plaque in the coronary arteries that can be countered by HT” appears to be at odds with the

apparent reluctance of many WHI investigators to consider that HT might be similarly cardioprotective when started at the time of menopause.

Worry about breast cancer has now emerged as the number one factor that deters women from seeking HT for vasomotor symptoms. Two factors appear to be responsible for this awareness and worry. As they approach menopause, women will often know or will have heard of another woman in the prime of life who has suffered premenopausal breast cancer, but they will rarely have heard of a woman similarly disabled by cardiovascular disease. On top of this, breast cancer awareness organizations have done a remarkable job of mobilizing women to take action, participate in fund raising, and be concerned about their own breast health. The fact is, however, that these two exposures to breast cancer awareness have left most women with a distorted perspective of the relative risks for breast cancer.<sup>8</sup>

A truer perspective can be gleaned from a table that appeared in the *New England Journal of Medicine*,<sup>9</sup> reproduced in the 2009 SOGC report.<sup>10</sup> This table shows that, at every decade of life, cases of breast cancer and deaths from breast cancer are eclipsed by other conditions. For example, in women aged 50 to 60 years, five of every 1000 women will die from breast cancer compared to 55 from other causes. This discrepancy is magnified in each succeeding decade, such that in women aged 70 to 80 years, nine of 1000 women will die of breast cancer compared with 309 from other causes.

This is not to imply that breast cancer is not a serious disease or that it does not warrant our attention. However, it should be emphasized that when physicians address risks of HT in counselling, they need to bring perspective to the discussion.

A recent comprehensive analysis of breast cancer news in leading media outlets found that articles on breast cancer risk factors tended to focus on HT, while ignoring equally important modifiable risk factors that could have a major impact on breast cancer rates in developing countries.<sup>11</sup> Debate continues about whether HT promotes earlier detection of pre-existing tumours (proponents of this view point out the return to normal cancer risk after stopping hormone therapy and the improved breast cancer survival among prior HT users<sup>12,13</sup>) or whether HT actually initiates new tumour development.<sup>14</sup> In any event, available evidence suggests that the overall impact of HT on the appearance of new breast cancers is small and compares to the risks of other modifiable lifestyle factors.<sup>15</sup>

Researchers, clinicians, and the media share an obligation to consider seriously the ramifications of research findings and the way in which they are disseminated to the public

and regulatory authorities. Recent experience with knowledge translation of research findings for hormone therapy of menopausal women has demonstrated the profound negative effect that sensationalism and exaggerated media attention can have. Physicians and consumers alike have downplayed the benefits of hormone therapy and exaggerated the potential adverse effects in the symptomatic, recently menopausal woman. New websites have sprung up to monitor the quality of reporting of medical stories.<sup>16</sup> We should expect nothing less in terms of rigour and responsibility from health care researchers and the journals in which they publish their findings.

“Research has shown that strong beliefs about risk, once formed, change very slowly and are extraordinarily persistent in the face of contrary evidence,” according to Vincent Convello from the Centre for Risk Communication at Columbia University.

The pendulum is swinging back, and reanalysis of the WHI data is providing reassurance that the reported HT-associated adverse events occurred largely in older women or long-term users. Just how damaging the negative publicity of the past several years has been, and how readily new, more reassuring, data on HT will be assimilated, remains to be seen. Will the present generation of 50-year-olds deny themselves the benefits of HT because of unfounded fears about the risks involved? The 2009 update on Menopause and Osteoporosis from SOGC examines the controversies surrounding HT and tries to frame the benefits and risks in a way that will be useful for practising clinicians and the women they serve.

## REFERENCES

- Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288(3):321–33.
- Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Writing Group for the Women's Health Initiative Investigators. Estrogen plus progestin and the risk of coronary heart disease. *N Eng J Med* 2003;349:523–34.
- Jane Brody. Sorting through the confusion over estrogen. *New York Times*. September 3, 2002. Available at: <http://query.nytimes.com/gst/fullpage.html?res=9907E0DE1E3FF930A3575AC0A9649C8B63>. Accessed November 5, 2008.
- Rossouw J, Prentice RL, Manson JE, Wu LL, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297(13):1465–77.
- Depypere HT, Tummers P, De Bacquer D, De Backer G, Do M, Dhont M. Number of women needed in a prospective trial to prove potential cardiovascular benefit of hormone replacement therapy. *Climacteric* 2007;10:238–43.
- Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133:933–41.
- Allison MA, Manson JE, Langer RD, Carr JJ, Rossouw JE, Pettinger MB, et al. Oophorectomy, hormone therapy, and subclinical coronary artery disease in women with hysterectomy: the Women's Health Initiative coronary artery calcium study. *Menopause* 2008;15(4 Pt 1): 639–47.
- Hart PL. Women's perceptions about coronary heart disease: an integrative approach. *J Cardiovasc Nurs* 2005;20(3):170–6.
- Fletcher SW, Elmore JG. Clinical practice. Mammographic screening for breast cancer. *N Engl J Med* 2003;348(17):1672–80.
- Reid RL, Blake J, Abramson B, Khan A, Senikas V, Fortier M. Menopause and Osteoporosis Update 2009. *J Obstet Gynaecol Can* 2009 Jan;31(1)(Suppl 1):S1–S48.
- Atkin CK, Smith SW, McFeters C, Ferguson V. A comprehensive analysis of breast cancer news coverage in leading media outlets focusing on environmental risks and prevention. *J Health Commun* 2008;13:3–19.
- Newcomb PA, Egan KM, Trentham-Dietz A, Titus-Ernstoff L, Baron JA, Hampton JM, et al. Prediagnostic use of hormone therapy and mortality after breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:864–71.
- Speroff L. Postmenopausal hormone therapy and the risk of breast cancer: a contrary thought. *Menopause* 2008; 15(2):393–400.
- Beral V. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362(9382):419–27.
- Singletary SE. Rating the risk factors for breast cancer. *Ann Surg* 2003;237:474–82.
- Media Doctor Canada [website]. Available at: <http://www.mediadoctor.ca>. Accessed November 4, 2008.