

## The HRT furore: getting the message right

*Research papers should have a short section on how the results should be communicated to the public*

BY ALL ACCOUNTS, many of the half million Australian women who regularly take combined oestrogen and progestin hormone replacement therapy (HRT) were alarmed by the news on Wednesday, 10 July 2002, reporting that a United States study had shown HRT to increase the risk of breast cancer by 26%, as well as causing more vascular disease. Subsequently, numerous media reports, based on press releases from organisations such as the US National Institutes of Health (NIH)<sup>1</sup> and the Cancer Council of New South Wales,<sup>2</sup> continued to highlight the apparently large increases in risks caused by combined HRT and called for restrictions on the use of this treatment. General practitioners and cancer help-lines were inundated by enquiries from frightened women and reports of mass withdrawals from therapy soon followed.

The source of this concern was the early termination of the NIH-funded Women's Health Initiative (WHI) trial comparing combined HRT and placebo among healthy postmenopausal women. The study was stopped after five years by an independent Safety and Data Monitoring Committee when a predetermined safety boundary for the risk of invasive breast cancer was crossed at an interim analysis. The report of the trial, published in *JAMA*,<sup>3</sup> suggested that women allocated to combined HRT experienced increased risks of invasive breast cancer, coronary heart disease, stroke and venous thromboembolism, and decreased risks of colorectal cancer and hip fracture (Box 1). It was argued that, when all these outcomes were summed in a "global index", the adverse effects outweighed the benefits.

However, treatment effects on only two of the outcomes — fractures and venous thromboembolism — met conventional criteria for statistical significance when appropriate (and prespecified) account was taken of the multiplicity of statistical tests performed. Even without adjustment for the dozens of statistical tests, the 95% confidence intervals for each of the other outcomes reportedly affected by combined HRT (including the global index) were consistent with a broad range of possible effects, including little or no effect. For example, any effect on the relative risk of invasive breast cancer appeared to lie somewhere in the range from no effect to an increase of about a half to two-thirds, whereas any effect on the absolute risk of the same outcome appeared to lie somewhere in the range from no excess cases to about 17 extra cases per 10 000 women per year. This very large degree of uncertainty about the true size (and arguably the existence) of most of the treatment effects reported is not reflected in any of the press releases we have seen, including that from *JAMA*,<sup>4</sup> all of which report apparently precise estimates of the excess risks.

However, the controversy that followed publicity about the results of the trial did not reflect concerns about the strength of the evidence, but rather dissatisfaction with the way in which the study outcomes were described. While the

### 1: Main results of the Women's Health Initiative trial of oestrogen plus progestin in healthy postmenopausal women<sup>3</sup>

Outcome	Hazard ratio*	Adjusted 95% CI†	Unadjusted 95% CI
Cardiovascular disease	1.22	1.00–1.49	1.09–1.36
Coronary heart disease	1.29	0.85–1.97	1.02–1.63
Stroke	1.41	0.86–2.31	1.07–1.85
Venous thromboembolism	2.11	1.26–3.55	1.58–2.82
Cancer	1.03	0.86–1.22	0.90–1.17
Invasive breast	1.26	0.83–1.92	1.00–1.59
Endometrial	0.83	0.29–2.32	0.47–1.47
Colorectal	0.63	0.32–1.24	0.43–0.92
Fractures	0.76	0.63–0.92	0.69–0.85
Hip	0.66	0.33–1.33	0.45–0.98
Vertebral	0.66	0.32–1.34	0.44–0.98
Deaths from other causes	0.92	0.62–1.35	0.74–1.14
Total deaths	0.98	0.70–1.37	0.82–1.18
Global index‡	1.15	0.95–1.39	1.03–1.28

\*Hazard ratios from Cox regression analyses of outcome among 8506 women randomly allocated to oestrogen plus progestin and 8102 women allocated to placebo. †Adjusted using group sequential methods to correct for multiple analyses over time. ‡First event for each participant from among the following: coronary heart disease, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death from other causes.

original report published in *JAMA* provided estimates of both relative-risk and absolute-risk differences, press releases from most sources focused on the relative increases in risk — in particular, the 26% increase in invasive breast cancer. That this increase in relative risk reflected a difference in incidence of eight cases per 10 000 women per year was much less emphasised. It was suggested by the economics editor of the *Sydney Morning Herald* that the reported 26% increase was likely to have been misinterpreted by many women as meaning that combined HRT conferred a one-in-four chance of developing invasive breast cancer.<sup>5</sup> Others argued that the use of relative risks in press releases was a deliberate effort to dramatise results that would appear much less newsworthy if described in absolute terms. The same commentators suggested that press releases should focus instead on absolute treatment effects, as these are of most direct relevance to the advice provided by doctors and the decisions made by women.

Are these criticisms justified? Certainly, there is little doubt that the way in which risk data are presented influences treatment preferences.<sup>6–9</sup> In a recent randomised trial in which general practitioners were asked whether they would prescribe a preventive treatment that had negligible side effects, 91% of those given information about relative

## 2: Essential statistical components for medical journal press releases describing the results of randomised clinical trials

### A. Provide estimates of absolute treatment effect in addition to estimates of relative treatment effect

- Estimates of relative treatment effect should not be provided without accompanying information about absolute treatment effect (or, at least, absolute disease rates).
- If the rates observed in the trial are substantively different from absolute disease rates in major patient subgroups, the limited generalisability of the observed absolute treatment effects should be acknowledged. For example, among perimenopausal women beginning hormone replacement therapy (HRT), whose average age is 10–15 years younger than those recruited to the Women's Health Initiative (WHI), any absolute increase in invasive breast cancer incidence is likely to be less than that observed in WHI, as breast cancer rates are strongly age related.

### B. Describe the full range of possible effects consistent with the observed result

- Avoid inappropriate focus on point estimates of either relative or absolute effect when confidence intervals indicate a broad range of potential effects. For example, the WHI result for invasive breast cancer risk was reported in press releases as a 26% increase in relative risk (and, occasionally, as an absolute excess of 8 cases per 10 000 women per year). However, the observed result is consistent with no increase in risk, as well as with an increase in relative risk of half to two-thirds and an increase in absolute risk of up to about 17 cases per 10 000 women per year (based on unadjusted 95% confidence intervals).

risks alone said they would do so, compared with 63% of those given information about absolute risks.<sup>6</sup> Other studies suggest that the way in which risk information is presented to consumers can generate even greater divergence in preferences.<sup>7</sup> Should we therefore abandon the use of relative risks entirely in interpreting the results of clinical trials? Almost certainly not — although a strong case can be made for not allowing relative risks to dominate press releases without appropriate reference to absolute risks. Arguably, each has a place in communications to doctors and patients, and neither should be relied upon exclusively, as both have strengths and weaknesses. For example, while relative risks are usually generalisable to a variety of different patient subgroups (since the proportional effects of treatments are often broadly similar in most major patient subgroups), absolute risks are not (since absolute effects are determined in large part by background disease risks, which can vary substantially). Conversely, relative-risk estimates do not provide sufficient information for assessing the ratio of benefit to harm, as this can only be calculated from estimates of absolute treatment effects.

Given the obvious complexity of identifying and delivering the most appropriate message to consumers (whether doctors or patients), medical journals might well consider taking a more substantive role in overseeing the broader dissemination of information about the results of major randomised trials. At a recent seminar (“*The HRT debate: how should the new evidence affect policy?*”) conducted by the Australian Health Policy Institute at the University of Sydney, it was suggested that research papers should have a short section on how the results should be communicated to

the public (Sally Crossing, Chair, Breast Cancer Action Group NSW, personal communication). Journals could assume more responsibility in two ways. Firstly, by ensuring compliance with a checklist of essential statistical components to be included in press releases issued by journals (Box 2); and secondly, by publishing a section within the main journal article that summarises the key messages for consumers, with reference to the same checklist. Such a checklist should include requirements for information about absolute as well as relative treatment effects, and for information about the full range of possible effects consistent with the observed result. If journals were to adopt this policy, it would be less likely that consumers would be misled, unintentionally or otherwise, by information released through the press. One can only speculate as to whether providing such information after the termination of the WHI would have altered the subsequent 30% fall in sales of the most commonly prescribed HRT preparations in Australia.<sup>10</sup>

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*Competing interests:* None identified.

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