SHORT REPORT

Simulation of a putative susceptibility risk factor to explain the findings of the Heart and Estrogen/progestin Replacement Study (HERS)

Bruce M. Psaty*, Mary Cushman† and Frits R. Rosendaal‡

Abstract

In the HERS trial, hormone therapy did not reduce the risk of coronary events. In *post hoc* analyses, treatment was associated with early harm and late benefit. According to one hypothesis, a risk factor may well distinguish a susceptible subgroup with early events associated with hormone therapy from a nonsusceptible subgroup who benefit from hormone therapy. In simulation studies, it appeared that only a susceptibility factor with a low prevalence (3–5%) and a high risk ratio (13–25-fold) can produce the pattern of risks seen in HERS. The number of candidate factors is likely to be small.

* Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology and Health Services, University of Washington, Seattle, WA, USA

† Departments of Medicine and Pathology, University of Vermont, Burlington, VT, USA

‡ Departments of Clinical Epidemiology and Hematology, Leiden University Medical Center, Leiden, the Netherlands

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Since observational studies have consistently suggested that the use of hormone replacement therapy in postmenopausal women reduces the risk of coronary heart disease,[1,2] the results of the Heart and Estrogen/progestin Replacement Study (HERS) were unexpected.[3] In this randomized clinical trial of secondary prevention, combined hormone therapy was no better than placebo at preventing coronary events in postmenopausal women (risk ratio [RR] = 0.99, 95% confidence interval [CI] = 0.81–1.22). In *post hoc* analyses, treatment was associated with a pattern of early harm and late benefit — a risk ratio of 1.52 (95% CI = 1.01–2.29) during the first year of follow-up and a risk ratio of 0.75 (95% CI = 0.50–1.13) during follow-up years 4 and 5.

While chance fluctuations around a null finding of 0.99 remain one important potential explanation,[4] the HERS investigators offered another broad hypothesis to explain this pattern of risks — the possibility of 'an immediate prothrombotic, proarrhythmic or proischemic effect of treatment that is gradually outweighed by a beneficial effect on the underlying progression of atherosclerosis'.[3] We recently reported an interaction between hormone replacement therapy and the prothrombin variant on the risk of myocardial infarction in hypertensive women.[5] If the hypothesis of an interaction with a risk factor that disposes to early harm is true, there may be a susceptible subgroup who have early events associated with hormone replacement therapy and another nonsusceptible subgroup who benefit from hormone replacement therapy. Identification of such a susceptibility factor would enable clinicians to target hormone therapy to those postmenopausal women who are most likely to benefit and avoid using it in those who might experience adverse events. An understanding of the likely characteristics of this hypothetical susceptibility factor, such as its prevalence and its effect size, might help in the search.

We undertook a series of simulation studies to estimate the prevalence of the susceptible subgroup and, if exposed to hormone replacement therapy, their risk ratio for coronary events — a combination of prevalence and risk that could reproduce the results of the HERS trial. In all simulations, we assumed that there were 1400 women in each arm of the trial and that the event rate was 30 coronary events per 1000 person-years in the control group. For the effect of oestrogens on risk ratio for coronary events in the nonsusceptible subgroup, we tried several assumptions: (i) risk ratios of 0.9 in year 1, 0.8 in year 2, and 0.7 in years 3–5; (ii) risk ratios of 0.75 in all years; and (iii) risk ratios of 0.70 in all years. This first set of assumptions was based loosely on the lipid-lowering trials, where the

Correspondence to Bruce M Psaty, MD, PhD, Cardiovascular Health Research Unit, 1730 Minor Avenue, Suite 1360, Seattle, WA 98101, USA
E-mail psaty@u washington edu

Table 1 Prevalence and risk ratio among susceptibles for hormone-replacement therapy in two simulations

	Simulation 1					Simulation 2				
Prevalence	RR	year 1	year 2	year 3	year 4–5	RR	year 1	year 2	year 3	year 4–5
	HERS =	1.52	0.98	0 85	0.75	HERS =	1.52	0.98	0.85	0 75
0 01	25	1 14	0 86	0 72	0 70	25	0 99	0 81	0 77	0 75
0 02	25	1 38	0 93	0 73	0 71	25	1 23	0 88	0 78	0 76
0 03	21	1 50	1 03	0 79	0 72	25	1 48	0 94	0 80	0 76
0 04	16	1 50	1 13	0 88	0 77	20	1 52	1 07	0 88	0 79
0 05	13	1 50	1 19	0 95	0 83	16	1 51	1 17	0 97	0 84
0 06	11	1 51	1 23	1 00	0 88	13	1 48	1 22	1 05	0 90
0 07	10	1 54	1 27	1 05	0 92	12	1 54	1 28	1 10	0 94
0 08	9	1 55	1 30	1 09	0 96	10	1 49	1 29	1 14	1 00
0 09	8	1 54	1 32	1 11	0 99	9	1 49	1 32	1 18	1 04
0 10	7	1 51	1 31	1 13	1 02	8	1 47	1 33	1 21	1 07

RR = risk ratio for coronary events among the susceptibles exposed to hormone replacement therapy In simulation 1, the risk ratios for coronary events among nonsusceptibles using hormone replacement therapy were assumed to be 0 9 in year 1, 0 8 in year 2, and 0 7 in years 3–5 In simulation 2, the risk ratios for coronary events among the nonsusceptibles using hormone replacement therapy were assumed to be 0 75 in each year Pascal source code and output for the simulations included in the table are available on request

survival curves separate only gradually over the first 1–2 years of the trial.[6]

In the simulations, we varied the prevalence of the susceptibility factor from 1% to 25% and the risk ratio for the effect of hormone replacement therapy on the risk of coronary disease from 1 to 25 in the susceptible group. In other words, each simulation included 625 combinations of a prevalence and a risk ratio. For each combination and for each year of follow-up, we calculated the numbers of events and subjects at risk in the treated group and the placebo group, and these numbers were used to estimate the overall risk ratio associated with hormone therapy during each year of follow-up. The event rate in the simulated placebo group was constant. In the simulated hormone replacement therapy group, the total number of events during any one year was the sum of the events in the large group (99–75%) of nonsusceptibles whose relative risk ranged from 0.9 to 0.7 in the various simulations and the events in the small group (1–25%) of susceptibles whose relative risk ranged from 2.0 to 25.0.

Table 1 summarizes the results of two simulations. The top line of Table 1 includes the findings from HERS, which we wished to duplicate in the simulation For each prevalence, one of the 25 simulated risk ratios was selected in an effort to reproduce the year 1 risk of 1.52 and the year 4–5 risk of 0.75. The question is really this: for which combination of prevalences and risks can the overall findings for the population be at once 1.52 in year 1 and 0 75 in years 4–5? In Table 1, the answer is not many. A susceptibility factor with a prevalences of 1–2%, even when risk ratios were 25, could not attain a year 1 level of risk of 1.52. A susceptibility factor with a prevalence of 3–5%, when the risk ratios were 13–25, provided perhaps the best fit. For a factor with a prevalence of 6–10%, when the estimated year 1 risks were close to 1.52, the year 4–5 risks were at or above 0.88. For prevalences above 10%, the year 4–5-values did not go below 1.0. Assuming the effect of hormone replacement therapy in the nonsusceptible group was 0 70 across all years shifted the best fit only slightly to prevalences of 4–6% with risk ratios of 20 to 16 (data not shown).

In this simulation, we assumed that a single fixed factor such as a genetic trait confers an increased coronary risk to a small subgroup who are exposed to hormone replacement therapy while the rest of the population experiences various levels of a modest benefit from hormone replacement therapy. Under this model, it appears that only a factor with a low prevalence and a high risk ratio can reproduce the pattern of risks seen in HERS. The number of candidate factors that meet these criteria is likely to be small.

This conclusion about the characteristics of the unknown susceptibility factor depends upon several assumptions. We assumed that there was only one susceptibility factor and that its risk ratio was constant over time. Moreover, we did not take into account a possible variability around these point estimates. Had we done so, the range of potential prevalences and risk ratios would have been larger. Indeed, sampling variability around the null of 0.99 is another reasonable explanation for the HERS findings. The model with a fixed factor would not be appropriate if multiple factors are involved, if the factor is one such as smoking, that may change with time, or if physiological adjustments modify the interaction over time.

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