The Reynolds Risk Score: How the WHS is improving cardiovascular risk prediction in women

Many factors are known to increase the risk for coronary heart disease. More than 40 years ago, investigators with the Framingham Heart Study identified several key risk factors and about 10 years ago used this knowledge to develop a tool to predict heart disease risk. Variations exist, but one version of the Framingham Risk Score relies on six pieces of information—age, gender, total cholesterol, HDL cholesterol, smoking status, and systolic blood pressure—to estimate one’s chance (risk) of having a first heart attack or being diagnosed with heart disease in the next 10 years. A risk greater than 20 percent is considered high; a risk of 10 to 20 percent is intermediate to high; a risk of 5 to less than 10 percent is low to intermediate; and a risk of less than 5 percent is very low.

An accurate assessment of cardiovascular risk is critical in helping doctors determine which prevention strategies to recommend for any particular patient. Striving for a heart-healthy lifestyle—e.g., avoiding saturated and trans fats, getting regular physical activity, and not smoking—is important for everyone regardless of risk level, and sufficient for those at low risk. Aspirin or medications that favorably affect cholesterol levels and blood pressure are likely to be helpful for people at intermediate cardiovascular risk and are definitely recommended for those at high risk.

Although widely used by doctors, the Framingham tool is not quite as good at predicting heart risk in women as it is in men. So, using the data from the more than 24,000 WHS participants who contributed a baseline blood sample, WHS researchers, led by Paul Ridker, MD, MPH, and Nancy Cook, ScD, set out to develop a new tool that would improve on the accuracy of the Framingham Risk Score while retaining its simplicity. How did they do this? First, they compiled a list of three dozen potential risk factors for heart disease and stroke. On the list were the traditional risk factors identified by the Framingham research team four decades ago as well as novel risk factors discovered by WHS and other investigators more recently. Next, they plugged the values for each of these risk factors from 16,000 of the aforementioned WHS participants into a computer model to determine which combination of factors would best predict whether these participants would go on to develop a heart attack, stroke, or other cardiovascular event during 10 years of follow-up. (More about the remaining 8,000 participants in a minute.)

Seven factors emerged as most predictive: age; smoking; systolic blood pressure; the inflammatory

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Announcing the Women’s Health Study website

The newly launched WHS website is located at http://whs.bwh.harvard.edu. The website will serve as a repository of information about the study and also allow us to relay study updates to participants on a more frequent basis than is possible via the annual newsletter. We are also exploring the feasibility of giving participants the option of completing their annual questionnaires online, using a link to a special, secure section of the website to ensure confidentiality. Stay tuned for more details.
Ongoing research projects

**Cancer Consortium**

WHS researchers are collaborating with other cancer research groups in the U.S. and Europe in the Cancer Consortium, an initiative funded by the National Cancer Institute to accelerate research on the role of gene-environment interactions in the development of cancer. Data from the WHS have been combined with data from eight other large studies of women and men to create a dataset of nearly 800,000 participants. Using this dataset, David Hunter, MBBS, ScD, and his consortium colleagues are currently investigating how variations in genes that control hormone production and function interact with hormonal and lifestyle factors to influence the risk of developing breast, pancreatic, total, fat, mono- and polyunsaturated fat, cholesterol, eggs, and calcium, as well as specific dietary foods, including milk, cheese, yogurt, and ice cream. However, a modest increase in ovarian cancer risk was seen with high intakes of saturated fat (intakes exceeding 21 percent of daily calories) and lactose (intakes equivalent to 3 or more servings of milk per day).

(Cancer Epidemiology, Biomarkers & Prevention 2005;14:2160-2167; British Journal of Cancer

We are using the data collected from WHS participants to address a wide variety of research questions.

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WHS: Advancing Scientific Knowledge About Women’s Health

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Recent findings from the WHS

- **Blood clots**
  
  Blood clots that form in leg veins (deep vein thrombosis) can be dangerous. Pieces of the clot can break off and travel through the veins to lodge in the lungs (pulmonary embolism), putting strain on the heart or even causing death. Heredity strongly affects a person’s susceptibility to forming blood clots. People with particular mutations in the genes for clotting factor V (that’s “V” as in “five,” and the mutation is called factor V Leiden) or clotting factor II (also known as prothrombin, and the mutation is known as the G20210A prothrombin mutation) overproduce these clot-promoting proteins, with the result that their blood clots very readily. Prolonged immobility (as on long airline flights), recent surgery and other bodily traumas such as bone fracture, and illnesses such as lupus, cancer, and heart failure also raise the risk of blood clots.

  Aspirin, which thins the blood, has been shown to prevent clots in high-risk surgical patients, but whether it also protects against clots in healthy women or in those with an inherited predisposition to developing clots is unclear. Researchers examined this question in the WHS and found that low-dose aspirin was not effective in preventing blood clots in the study population as a whole or in those at high risk of clots because of factor V Leiden or the G20210A prothrombin mutation. (These mutations, one or both of which were found in nearly 8 percent of WHS participants, increased the risk of blood clots by about threefold.) (Glynn RJ et al., Annals of Internal Medicine 2007;147:525-533.) On the other hand, data from the WHS suggest that vitamin E supplementation may reduce the risk of blood clots, particularly in women with a prior history of or genetic predisposition towards clotting. In the WHS study population as a whole, women assigned to vitamin E were 21 percent less likely to have a blood clot than women assigned to placebo. Among women with a history of blood clots at study entry, vitamin E was associated with a 44 percent reduction in risk. Among women with factor V Leiden or the G20210A prothrombin mutation, the corresponding reduction was 49 percent. The biologic reason for the apparent protective effect is unclear, but vitamin E is known to interfere with the action of vitamin K, a vitamin required for normal blood clotting (Glynn RJ et al., Circulation 2007;116:1497-1503).

- **Type 2 diabetes**
  
  Type 2 diabetes, a metabolic disorder characterized by excess sugar in the blood that results from defects in the action of insulin (a hormone produced by the pancreas), affects 8 percent of U.S. adults. In addition, an estimated 40 percent have pre-diabetes, a condition in which blood sugar levels are somewhat elevated but not high enough to be classified as full-fledged diabetes. Type 2 diabetes is the main cause of kidney failure, limb amputations, and adult-onset blindness in the U.S., and is a major risk factor for coronary heart disease and stroke.

  Studies in animals and of pancreatic cells, as well as small clinical trials in patients with type 2 diabetes, have found that administration of vitamin E can boost insulin secretion and improve insulin action, leading to the hypothesis that this vitamin can prevent the development of diabetes in healthy individuals. However, the WHS—the only large-scale trial to test this hypothesis—found no evidence to suggest that vitamin E protects against type 2 diabetes (Liu S et al., Diabetics 2006;55:2856-2862). WHS analyses regarding the relation between aspirin and risk of type 2 diabetes are underway and will be reported in next year’s newsletter.

- **Cognitive decline**
  
  As we grow older, many of us worry about memory loss. Although much research has been done on medications that may prevent further cognitive decline among persons with dementia, few studies have tested interventions that may keep the brains of healthy individuals sharp. In 1998, WHS researchers initiated a study of memory and thinking among WHS participants aged 65 and older to test whether low-dose aspirin and vitamin E supplementation could stave off cognitive decline. More than 6,000 participants completed a 10-minute telephone interview consisting of standard memory and cognitive function tests on three separate occasions spanning a four-year interval. Neither aspirin nor vitamin E supplementation was effective at slowing cognitive decline in these women (Kang JH et al., British Medical Journal 2007;334:4987; Kang JH et al., Archives of Internal Medicine 2006;166:2462-2468).

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By combining the data from more than two dozen large studies of women and men in North America, Europe, and Asia, investigators hope to gain a better understanding of the association between diet and various cancers. This strategy is particularly useful for studying rare cancers such as ovarian cancer because it maximizes the number of cancer cases available for analysis. To date, approximately 2100 cases of ovarian cancer have occurred among the more than 560,000 women enrolled in the participating studies. Using this dataset, investigators have found that risk of ovarian cancer appears to be unrelated to a number of dietary factors, including intake of fruits, vegetables, alcohol, total fat, mono- and polyunsaturated fat, cholesterol, eggs, and calcium, as well as specific dairy foods, including milk, cheese, yogurt, and ice cream. However, a modest increase in ovarian cancer risk was seen with high intakes of saturated fat (intakes exceeding 21 percent of daily calories) and lactose (intakes equivalent to 3 or more servings of milk per day).

(Cancer Epidemiology, Biomarkers & Prevention 2005;14:2160-2167; British Journal of Cancer

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REYNOLDS RISK SCORE—continued

marker C-reactive protein (CRP); having a parent who developed heart disease before age 60; and two cholesterol-related measures, apolipoprotein B and apolipoprotein A-I. Apolipoprotein B and apolipoprotein A-I are closely linked to total cholesterol and HDL cholesterol, respectively, so the researchers substituted the more widely used measures. These substitutions make the new tool nearly as easy to use as the Framingham Risk Score in that it requires only one additional blood test (that for CRP).

As a last step, WHS researchers tested the tool in the remaining 8,000 WHS participants who had contributed a baseline blood sample. It did as well as the Framingham Risk Score for women in the lowest and highest risk groups. But it outperformed the Framingham Risk Score for those in the middle two risk groups, reassigning nearly half these women into higher or lower risk categories. The new classifications better predicted whether or not these women actually developed heart disease or stroke over the next 10 years. The findings were reported in the February 14, 2007 issue of the Journal of the American Medical Association (JAMA 2007;297:611-619).

“The new tool, dubbed the Reynolds Risk Score after the foundation that funded this research, contains all the factors deemed important 40 years ago from the Framingham Heart Study, plus two measures that represent major advances in our understanding of the origins of cardiovascular disease,” said Dr. Ridker. “The inclusion of CRP reflects the fact that inflammation is intimately connected to cardiovascular disease. The inclusion of family history signifies the importance of genetics.”

“Our hope is that, by more accurately classifying patients with respect to cardiovascular risk group, doctors will be better able to target the use of aspirin or cholesterol-lowering medications,” he added.

To calculate your Reynolds Risk Score, visit www.reynoldsriskscore.org, or ask your healthcare provider to do so. (For your Framingham Risk Score, go to http://hin.nhlbi.nih.gov/atpiii/calculator.asp.) Learning that you are at low cardiovascular risk is reassuring, but that knowledge is not carte blanche to abandon—or refrain from adopting—heart-healthy habits. Findings from the Framingham Heart Study suggest that a 50-year-old woman with a healthy heart has a 40 percent risk of developing heart disease as she grows older. Vigilance in monitoring and controlling your risk factors will cut your odds of developing heart disease later in life.

Seven factors emerged as most predictive: age, smoking, systolic blood pressure, the inflammatory marker C-reactive protein (CRP), having a parent who developed heart disease before age 60, and two cholesterol-related measures.

A query to WHS Update readers

Are there topics related to women’s health that you would like to see addressed in this newsletter, or experiences related to your participation in WHS that you would like to share with other women? If so, please let us know!

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2006;94:757-762; Cancer Causes and Control 2006;17:273-285; Cancer Epidemiology, Biomarkers & Prevention 2006;15:364-372.)

• Women’s Genome Health Study

WHS researchers, led by Paul Ridker, MD, MPH, have partnered with the National Heart, Lung, and Blood Institute to conduct full genome scans on WHS participants who donated a blood sample at the beginning of the study. The goal of the Women’s Genome Health Study is to refine cardiovascular risk prediction by adding specific genetic information to the Reynolds Risk Score (see page 1). The study also aims to identify genetic factors that influence the development of diabetes, cancer, osteoporosis, and cognitive decline. Watch for results of this landmark undertaking, which was initiated in October 2006, in future newsletters. Please be assured that all genetic data collected in the Women’s Genome Health Study are fully confidential, as are all blood data from the WHS.