4. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis. *JAMA*. 2011;305(6):569-575.

5. Morrow M, Van Zee KJ, Patil S, et al. Axillary dissection and nodal irradiation can be avoided for most node-positive Z0011-eligible breast cancers. *Ann Surg*. 2017;266(3):457-462.

6. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.11470

7. Grundy SM, Knowles JW. How studying familial hypercholesterolemia resulted in the discovery of statins as an effective treatment for high cholesterol. http://jamanetwork.com/learning/audio-player/14605193. Accessed August 11, 2017.

8. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis. *JAMA*. 2015;313(23):2340-2348.

Menopausal Hormone Therapy
Understanding Long-term Risks and Benefits

Melissa McNeil, MD, MPH

The influence of hormone therapy on the health of women has been a subject of controversy for decades. In the 1960s, when estrogen therapy was first introduced for the treatment of menopausal symptoms, hormones were viewed as a fountain of youth. One of the early hormone advocates, Robert Wilson in his 1966 book about menopause and hormones, stated that "Instead of being condemned to witness the death of their own womanhood, [women] will remain fully feminine—physically and emotionally—for as long as they live-...*Menopause is curable*."[1] What followed was a decade of unmitigated prescribing of unopposed estrogen (ie, without progesterone) for menopausal women both with and without a uterus. It then became clear that unopposed estrogen given to a woman with an intact uterus increased the risk of endometrial cancer,[2] and hormone therapy fell from favor in the 1970s. This was followed by a resurgence of interest in hormone therapy when it became apparent that the administration of progesterone with estrogen could mitigate the increased risk of endometrial cancer.

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By the 1980s, hormone therapy was widely prescribed both for symptom management as well as for prevention and treatment of osteoporosis.[3] The 1990s ushered in the widespread belief that hormone therapy was beneficial in reducing the burden of cardiovascular disease and offered the potential for a reduction of overall mortality among hormone users compared with nonusers.[4] The 10-year period between 1990 and the publication of the initial Women's Health Initiative (WHI) hormone therapy trials[5,6] was the golden era of hormone use with both symptom management and promise of a longer, healthier life attributed to hormone therapy.

The initial WHI hormone therapy trials,[5,6] especially the trial involving estrogen plus progestin, completely changed the understanding of the risks and benefits of hormone therapy and reinforced the importance of assessing numerous outcomes. Cardiovascular disease risk was increased rather than decreased as was the risk of thromboembolic disease. The relationship of hormone therapy to breast cancer was complex and confusing, and for the first time, differences in outcomes other than endometrial cancer risk were identified based on the administration of combination hormone therapy vs estrogen alone, with combination therapy increasing the likelihood of breast cancer and estrogen alone seemingly having no effect. In addition, instead of a reduction in mortality, there was no significant effect on life expectancy among hormone users vs nonusers. More questions than answers were raised including (1) why were the mortality results of previous cohort studies (such as the Nurses' Health Study[4]) so different from the results of the WHI randomized trials; (2) why were the outcomes from combination therapy with estrogen plus progestin compared with estrogen alone different; and (3) are there differences in the health benefits of hormone therapy for women based on the age or time since menopause when the hormone therapy was started/ The only certainty is that controversy remains as to the risks and benefits of different hormone therapy preparations for women of different risk profiles.

In this issue of *JAMA*, Manson and colleagues[7] report findings on the association of hormone therapy in the WHI trials with long-term all-cause and cause-specific mortality. As the authors of this study point out, given the complex interplay of hormone therapy with different health outcomes, all-cause and cause-specific mortality provide an important summary measure for both patients and physicians and provide much needed information to help with decision making. Previous counseling recommendations have focused on individual disease outcomes and have not provided sufficient information about the overall long-term risk/benefit ratio of hormone therapy, and many women have shied away from using hormone therapy and their physicians have been reluctant to prescribe this treatment because of concerns of long-term hazards of hormone use. The results of this analysis provides new and helpful data to inform decision making and to address this concern.

The authors assessed mortality outcomes in the 27 347 women who were randomized in the WHI trials, including those in one trial who received estrogen plus progesterone acetate (n = 8506) vs placebo (n = 8102) for 5.6 years (median) and those in the other trial who received estrogen alone (n = 5310) vs placebo (n = 5429) for 7.2 years (median). During 18 years of cumulative follow-up, a total of 7489 deaths

occurred. In the overall pooled cohort of all hormone users vs placebo, there was no difference in all-cause mortality between hormone users and nonusers (27.1% vs 27.6%; hazard ratio [HR], 0.99 [95% CI, 0-94-1.03]).[7] The results were similar for cardiovascular disease (CVD) mortality, with death rates from CVD in the pooled cohort of 8.9% in the hormone therapy group vs 9.0% in the placebo group (HR, 1.00 [95% CI, 0.92-1.08]) and for coronary heart disease and stroke mortality, suggesting no positive or negative association between hormone therapy and long-term CVD mortality. In addition, there were no differences in all-cause mortality based on either the combination of estrogen plus progesterone therapy vs placebo or estrogen therapy vs placebo, providing reassurance that short-term use of either hormone therapy regimen does not increase downstream risks later in life in terms of overall mortality. However, there were also no long-term reductions in all-cause mortality among women who used hormone therapy.

The effect of hormone therapy on cancer mortality, especially breast cancer mortality, has also been a subject of discussion and has generated concern for patients and physicians about hormone therapy administration, resulting in a reluctance to prescribe and also take hormone therapy for troubling menopausal symptoms. The current report by Manson et al[7] provides substantial reassurance for patients and physicians about this issue. During the 18 years of follow-up, there were 2207 deaths from cancer in the overall pooled cohort, and cancer mortality rates were almost identical between hormone users and nonusers (8.2% vs 8.0%; HR, 1.03 [95% CI, 0.95-1.12]).

With regard to breast cancer mortality, while no significant differences were seen between nonusers and users with any type of hormone therapy, the heterogeneity in the results between combination therapy users and estrogen-only users precluded pooled data results. For combination hormone therapy users, the breast cancer mortality HR was 1.44 (95% CI, 0.97-2.15) and for estrogen-alone users, the HR was 0.55 (95% CI, 0.33-0.92). Even though the differences in breast cancer mortality between combination hormone therapy users and estrogen-only users are not statistically significant, they are intriguing. The authors caution against too much reliance on *P* values for the interpretation of data given the multiple comparisons performed raising speculation that as the short-term data has suggested, there may be a difference in breast cancer outcome between the 2 hormone therapy regimens. Regardless, the take-home message is that all-cause cancer mortality was not affected by hormone therapy use in long-term follow-up and should be helpful for both patients and physicians.

Although the long-term data on total and cause-specific cumulative mortality of pooled data for hormone users vs nonusers is both compelling and reassuring, several questions remain. Perhaps the most challenging question involves the issue of whether there is a difference in overall mortality by age and menopausal status at the time of initiation of hormone therapy. A recent Cochrane review of randomized clinical trial data found a decreased risk of coronary heart disease (relative risk [RR], 0.52 [95% CI, 0.29-0.96]) among hormone therapy users when hormones were initiated less than 10 years after the onset of menopause.[8] There was no increase in stroke risk, and a reduction in all-cause mortality (RR, 0.70 [95% CI, 0.52-0.95]) was observed. However, this systematic review did not include the new long-term mortality data from the WHI, which is the largest randomized trial to address this question and has the longest follow-up.

The data on risks and benefits of hormone therapy according to age and time since menopause at the time of initiation of hormone therapy reported in the study by Manson et al[7] remain inconclusive. All-cause mortality was examined in the pooled cohort by 10-year age intervals both during the intervention phase (the time of the original study) and during the cumulative 18-year follow up. For women aged 50 to 59 years at the initiation of hormone therapy compared with women aged 70 to 79 years, the all-cause mortality in the pooled cohort during the intervention phase was significantly reduced (HR, 0.61 [95% CI, 0.43-0.87]). This reduction in mortality was still present at 18 years but failed to meet statistical significance (HR, 0.87 [95% CI, 0.76-1.00]) and thus remains suggestive but not definitive. Other questions that remain include the optimal duration of hormone therapy and if an even earlier initiation of hormone therapy, such as within 2 years of the menopausal transition, would provide additional benefits.

Overall, the results of this study from the WHI trials by Manson and colleagues[7] in this issue of *JAMA* expand the understanding of the long-term risks and benefits of hormone therapy, an important issue for women around the world. The findings provide reassurance that there is no long-term increase in either all-cause or cause-specific mortality among women who received hormone therapy for up to 5.6 years (combination estrogen plus progestin hormone therapy group) or 7.2 years (estrogen-alone group). This information will be helpful in counseling women considering whether to start hormone therapy and hopefully will alleviate concerns that many patients and physicians have about the initiation of hormone therapy. For women with troubling vasomotor symptoms, premature menopause, or early-onset osteoporosis, hormone therapy appears to be both safe and efficacious. The data presented by Manson et al[7] fully support the newly released 2017 hormone therapy position statement of the North American Menopause Society[9] and are a welcome addition to current knowledge regarding hormone therapy administration.

ARTICLE INFORMATION

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REFERENCES

1. Wilson RA. *Feminine Forever*. New York, NY: Pocket Books; 1968.

2. Gray LA Sr, Christopherson WM, Hoover RN. Estrogens and endometrial carcinoma. *Obstet Gynecol*. 1977;49(4):385-389.

3. Christiansen C, Riis BJ. 17 Beta-estradiol and continuous norethisterone: a unique treatment for established osteoporosis in elderly women. *J Clin Endocrinol Metab*. 1990;71(4):836-841.

4. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med*. 1991;325(11):756-762.

5. Rossouw JE, Anderson GL, Prentice RL, 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):321-333.

6. Anderson GL, Limacher M, Assaf AR, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701-1712.

7. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the Women's Health Initiative randomized trials. *JAMA*. doi:10.1001/jama.2017.11217

8. Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Sys Rev*. 2015;(3):CD002229.

9. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24(7):0000000000000921.

The Durability of Antireflux Surgery

Stuart J. Spechler, MD

Patients who have mild, nonerosive gastroesophageal reflux disease (GERD) have many valid treatment options, but patients with severe erosive GERD (those with endoscopy showing large esophageal mucosal breaks extending between mucosal folds) have only 2: take proton pump inhibitors (PPIs) indefinitely or have antireflux surgery with fundoplication.[1] No medication other than PPIs (and potassium-competitive acid blockers, which are not available in the United States) reliably heals reflux esophagitis; once healed, that esophagitis will return quickly and severely in most cases if PPIs are stopped.[2] Endoscopic antireflux treatments and other antireflux devices generally have been used to treat only milder forms of GERD, and their efficacy for healing severe erosive esophagitis has not been established. Increasing awareness that patients taking PPIs often have persistent GERD symptoms even though their esophagitis has healed and recent concerns regarding serious potential consequences of long-term PPI therapy have stimulated renewed interest in antireflux surgery. One key and contentious issue is the durability of fundoplication.

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Unlike PPIs that block gastric acid secretion but do not correct the underlying reflux diathesis, fundoplication creates a mechanical barrier to gastroesophageal reflux. Nissen fundoplication was described in 1956, and by the 1980s, when small series demonstrated greater than 90% efficacy for fundoplication in controlling GERD symptoms over a 10-year period, surgeons had come to regard the operation as a permanent cure for GERD.[3] A multicenter randomized trial conducted by the US Veterans Administration (VA) in the late 1980s (when antireflux surgery was performed as an open procedure and before PPIs were available) found that open Nissen fundoplication was significantly more effective than ranitidine-based medical therapy in healing the symptoms and endoscopic signs of complicated GERD for the 2-year duration of the study.[4] Laparoscopic fundoplication was introduced in 1991, and the less invasive laparoscopic approach soon became the standard for antireflux surgery.

These events fueled interest in antireflux surgery, and the number of such operations performed in the United States increased from 12 661 in 1994 to 31 695 in 1999.[5] But the level of interest decreased abruptly with the *JAMA* publication of long-term results of the aforementioned VA trial in 2001.[6] After a follow-up period of 10 to 13 years, 23 (62%) of the 37 surgical patients for whom follow-up was available reported that they were once again taking medications on a regular basis to treat their GERD symptoms. This study raised serious doubts regarding the durability of fundoplication, doubts that likely contributed to the 30% decline in the number of antireflux operations performed in the United States from 1999 to 2003.[5]

Studies that have focused on the durability of modern, laparoscopic antireflux surgery have found a wide range of GERD recurrence rates. Some cohort studies (involving up to 844 patients with follow-up periods of ≥2 years) found high rates of postoperative antireflux medication use, ranging from 33% to 43%.[7,8] Lower GERD recurrence rates (10%-15% during follow-up periods of 3-5 years) were found in several randomized trials of laparoscopic antireflux surgery vs medical therapy.[9] Although such randomized trials are considered high-quality clinical evidence, it is not clear how well they reflect clinical practice because they were performed at specialized centers and involved highly selected patients.

In this issue of *JAMA*, Maret-Ouda and colleagues[10] report the results of a retrospective, population-based cohort study of 2655 patients identified in the Swedish Patient Registry as having had primary laparoscopic antireflux surgery performed between 2005 and 2014. The investigators defined reflux recurrence as the postoperative use of PPIs or histamine 2 receptor antagonists (H_2RAs) for at least 6 months, or the performance of secondary antireflux surgery. During a mean follow-up period of 5 years, 470 patients (17.7%) had a reflux recurrence (393 used PPIs/H_2RAs, 77 had repeat surgery). Risk factors for recurrence were female sex, older age, and comorbidity. A subgroup of 559 men without comorbidity and aged 45 years or younger had a lower reflux recurrence rate of 11.1%.

Within 30 days of surgery, 109 of the total 2655 patients (4.1%) had complications such as infection, bleeding, and esophageal perforation. There were only 2 deaths (0.1%), neither of which was directly related to the operation. Dysphagia was documented in 21 patients (0.8%), including 14 (0.5%) who were treated with endoscopic dilatation.