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Insights into Male Breast Cancer

Overall survival was significantly worse for men with breast cancer than for their women counterparts.

Clinicians have been taught, with some caveats, that treatments and outcomes are very similar between men and women with breast cancer. However, recent studies have called this assumption into question.

Now, investigators have conducted a large cohort study using National Cancer Database (NCDB) data to compare mortality and methodologies between 16,000 men and 1.8 million women with breast cancer during a 10-year period. Men were older than women counterparts (63.3 vs. 59.9 years) and more likely to have ductal histology, higher-stage disease at diagnosis (stage III, 14.0% vs. 8.9%; stage IV, 5.8% vs. 3.8%), ER-positive disease, and higher recurrence score.

At a median follow-up of 54 months for men and 60 months for women, overall survival (OS; the primary outcome) was poorer for men than women (45.8% vs. 60.4%; $P < 0.001$), as was 3-year survival (86.4% vs. 91.7%; $P < 0.001$) and 5-year OS (77.6% vs. 86.4%; $P < 0.001$). Although men had more advanced disease and aggressive clinical characteristics, they were less likely to receive optimal conventional therapy, including endocrine or radiation therapy. After all factors were controlled for, male sex remained an independent factor associated with a poorer prognosis.

COMMENT: This study raises issues regarding male breast cancer that require further investigation, particularly the suggestion that simply being male results in a worse outcome. The authors acknowledge that cancer-specific mortality is difficult to obtain from NCDB data and that information was absent regarding compliance with treatment recommendations, genetics, and comorbidities.

CITATION(S): Wang F et al. Overall mortality after diagnosis of breast cancer in men vs women. *JAMA Oncol* 2019 Sep 19; [e-pub]. (<https://doi.org/10.1001/jamaoncol.2019.2803>)

Estrogen-Progestin Therapy Elevates Risk for Breast Cancer — Should This Influence Clinical Practice?

Andrew M. Kaunitz, MD and JoAnn E. Manson, MD, DrPH

No; benefits will outweigh risks for many menopausal patients who, through discussion of research findings and shared decision making, can make informed choices about HT use.

Hormone therapy (HT) is the most effective treatment for bothersome menopausal vasomotor symptoms. However, after initial publication of findings from the Women's Health Initiative (WHI) randomized clinical trial in 2002, which found that estrogen-progestin therapy (EPT) increased risk for cardiovascular events and breast cancer among women aged 50 to 79 at enrollment (*NEJM Journal Watch Womens Health Nov 2013* and *JAMA* 2013 Oct 2; 310:1353), use of HT plummeted in the U.S. and globally. Subsequently, the estrogen-alone trial in women with hysterectomy showed that conjugated estrogens (for a median of 7 years) did not increase breast cancer risk. Both regimens raised risk for stroke and venous thromboembolism but lowered risk for fractures and diabetes. Thus, HT has a complex risk-benefit pattern, with studies suggesting more-favorable profiles in younger than older women.

Although observational studies over the past several decades have linked HT to increased breast cancer risk, the specific associations with HT formulation, route of delivery, and duration have been poorly studied. In a recent meta-analysis (*Lancet Aug 29 2019 [e-pub]*), investigators used individual participant data from 58 observational studies reported between 1992 and 2018 to quantify the strength of the relation and the roles of these factors in the HT–breast cancer connection.

All systemic HT formulations (including those using oral conjugated equine estrogens or estradiol or transdermal estradiol) were associated with excess risk for breast cancer. Use of EPT was associated with a greater risk for breast cancer than was estrogen-only therapy (ET). Type of progestogen did not appear to affect these associations. Vaginal estrogen was not associated with increased risk. Assuming the reported associations are causal, the authors estimated the absolute risk for breast cancer up to age 70. For never-users of HT and women who initiated EPT at age 50 and continued for 5 years, risks were 6.3% and 8.3%, respectively; the two percentage-point difference indicates one additional breast cancer case per 50 treated women. At 10 years of HT use, risks were approximately twice that at 5 years.

For EPT, both the randomized WHI trial and this new *Lancet* analysis of observational data indicated an increased risk for breast cancer. However, in contrast to the *Lancet* report, the WHI did *not* find that ET (conjugated equine estrogens alone) increased this risk — in fact, risk was significantly reduced after long-term follow-up. Could the excess risk found in observational studies be exaggerated due to inherent limitations of the study design? In observational settings, women using HT tend to undergo mammographic screening more frequently and consistently than nonusers. In contrast, in the WHI trial (and in most randomized trials of HT), both users and nonusers underwent uniformly standardized mammographic screening. Thus, the excess breast cancer risk in observational studies could reflect increased mammographic detection of nonlethal cancers. In addition, breast cancer incidence appears to increase with longer-duration HT use. Accordingly, one advantage that observational studies have over randomized trials (usually limited to 5–7 years of treatment) is their ability to assess extended use. The differences in mammographic screening between users and nonusers of HT are likely to persist and may even increase cumulatively over follow-up.

Wrap-Up: Understandably, women are often concerned about breast cancer risk as they make decisions about HT; however, such decisions should be guided by the big picture. On an absolute scale, many of the risks associated with HT are modest. Furthermore, with 18 years' cumulative follow-up, the WHI's findings on total mortality as well as overall cancer mortality with HT use are reassuring, especially for women younger than 60 (NEJM Journal Watch Womens Health Oct 2017 and JAMA 2017 Sep 12; 318:927). The largest hazard ratio associated with HT use corresponds to an elevated risk for venous thromboembolism — and using transdermal rather than oral estrogen appeared to attenuate this risk.

For many women, risks associated with HT are offset by reductions in symptoms, improved quality of life, and benefits in other health outcomes, such as fractures. The net effects of HT are most favorable for recently menopausal women who have moderate to severe vasomotor symptoms and low or average risks for breast cancer, cardiovascular disease, and venous thromboembolism. Women at above-average risk for the latter conditions may want to avoid HT and consider nonhormonal options for symptom management. In sum, women deserve reliable information in order to make informed decisions — aligned with their personal preferences — on whether the potential benefits of HT are likely to outweigh the potential risks.

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Estrogen-Only Systemic HT in the Setting of Bilateral Salpingo-Oophorectomy — Safe or Risky?

The answer is multifaceted: Outcomes of HT varied by women's age and BSO status.

To clarify the health effects of estrogen-only systemic hormone therapy (HT) in postmenopausal women without a uterus who did or did not undergo bilateral salpingo-oophorectomy (BSO), Women's Health Initiative researchers conducted an 18-year follow-up study involving 9939 women (age range, 50–79) who had been randomized to conjugated equine estrogen (CEE; 0.625 mg daily) or placebo for a median 7.2 years. Endpoints included coronary heart disease, invasive breast cancer, all-cause mortality, and a composite of serious health events (stroke, pulmonary embolism, colorectal cancer, and hip fracture).

Among women aged 50 to 69 without a uterus, systemic estrogen-only HT compared with placebo did not significantly raise risk for serious health events during treatment or long-term follow-up. Among younger women (age range, 50–59) who underwent BSO at hysterectomy, estrogen treatment was associated with a significant decrease in all-cause mortality during long-term follow-up (hazard ratio, 0.68; 95% confidence interval, 0.48–0.96). This mortality reduction was not observed among younger estrogen-treated women with hysterectomy but no BSO (HR, 0.93; 95% CI, 0.71–1.20). Among women aged 70 to 79 with BSO, risk for serious health events was significantly increased during estrogen treatment (HR 1.42, 95% CI 1.09–1.86); this excess risk was no longer statistically significant in cumulative follow-up (HR, 1.12; 95% CI, 0.94–1.34).

COMMENT; These results show that, in postmenopausal women without a uterus, systemic estrogen-only HT appears to be safe for those aged 50 to 69, both during treatment and after stopping or tapering such treatment. Among the subset of those aged 50 to 59 with BSO at hysterectomy, estrogen-only HT appears to reduce all-cause mortality during long-term follow-up; hence, these women should consider the potential health benefits of estrogen therapy. However, in women who are 70 or older, great caution should be exercised when initiating systemic estrogen therapy. I have never begun systemic

estrogen for such women — and in those who started this treatment earlier (e.g., near menopause onset) and continue to take it after age 70, I try to taper the estrogen dose with the goal of stopping therapy. Lastly, it's worth noting that vaginal estrogen therapy for genitourinary syndrome of menopause is safe for postmenopausal women at all ages ([NEJM JW Womens Health Feb 2019](#) and [Menopause 2019 Jun; 26:603](#)).

Andrew M. Kaunitz, MD, is an author of this study and Editor-in-Chief of *NEJM Journal Watch Women's Health* but had no role in selecting or summarizing this article.

CITATION(S): Manson JE et al. Menopausal estrogen-alone therapy and health outcomes in women with and without bilateral oophorectomy: A randomized trial. *Ann Intern Med* 2019 Sep 10; [e-pub]. (<https://doi.org/10.7326/M19-0274>)

Antidepressant Use in Pregnancy Linked to Gestational Diabetes

By Kelly Young Edited by [David G. Fairchild, MD, MPH](#)

Antidepressant use during pregnancy is associated with increased risk for gestational diabetes, according to a case-control study in *BMJ Open*.

Using a Canadian registry, researchers matched roughly 21,000 singleton pregnancies in which gestational diabetes developed to over 200,000 in which gestational diabetes did not occur. Women with obesity, type 1 or 2 diabetes, or prior gestational diabetes were excluded.

Any antidepressant use in pregnancy was associated with a modestly higher risk for developing gestational diabetes (adjusted odds ratio, 1.19). In terms of drug class, increased risks were seen with serotonin-norepinephrine reuptake inhibitors (aOR, 1.27) and tricyclic antidepressants (1.47). For particular agents, venlafaxine (1.27) and amitriptyline (1.52) conferred increased risk. Use of two or more antidepressant classes or two or more individual drugs was also associated with increased risk.

The authors write that antidepressant use can affect glucose homeostasis, pancreatic insulin secretion, cellular insulin resistance, and weight. They conclude: "Adverse outcomes associated with [antidepressant] use during pregnancy including [gestational diabetes] should be weighed against the consequences of non-medicated depression, especially for women with severe depression."

LINK(S): [BMJ Open article](#) (Free)

[JAMA Pediatr 2019 Sep 30](#)

Parent-Toddler Interactions when Reading Tablets vs. Print Books

Toddlers and parents were more likely to have controlling, intrusive, and isolating behaviors when trying to read a tablet together.

The American Academy of Pediatrics recommends that parents interact with children using digital devices such as smartphones and tablets, but the character of those interactions has not been described well.

Researchers video-recorded 37 parent-child dyads while each parent read a print book, a basic tablet-based book, and an enhanced tablet-based book (with interactive features) sequentially with their 24- to 36-month-old child. The order of

books varied randomly among dyads. The frequency of control behaviors (child closing or grabbing the book, child or parent pivoting away), intrusive behaviors (child or parent pushing the other's hand away from the book), and solitary space-making by the child was determined for each type of book.

Control and intrusive behaviors by children and parents were significantly more common while reading either of the tablet-based book formats than while reading print books. Specifically, children more frequently closed the digital books, pivoted away from the parent while holding the book, and pushed their parent's hand; parents pivoted away and pushed the child's hand more often. Children also assumed a posture that shielded the parent from the book more frequently.

COMMENT: The behaviors observed in this study will be recognizable to anyone who has tried to share a digital device with a young child. The results suggest two points: (1) when recommending that parents read every day with their children from birth onward, we should specify that print books provide an especially good way to interact, and (2) when talking with parents about interacting with toddlers using digital devices, we can advise they look for apps specifically made for socially reciprocal interactions, such as turn-taking. Finally, we can highlight how nondigital play leads to important interactions that are not common when devices are at hand.

Jenny Radesky, MD, is an author of this study and a member of the *NEJM Journal Watch Pediatrics and Adolescent Medicine* board but had no role in selecting or summarizing this article.

CITATION(S): Munzer TG et al. Parent-toddler social reciprocity during reading from electronic tablets vs print books. *JAMA Pediatr* 2019 Sep 30; [e-pub]. (<https://doi.org/10.1001/jamapediatrics.2019.3480>)

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Peanut Oral Immunotherapy for Peanut Allergy

Oral immunotherapy produces temporary desensitization in most patients but does not cure peanut allergy.

Studies have shown that oral immunotherapy (OIT) is effective at desensitizing patients to peanut allergen, but we don't know whether this can lead to permanent tolerance. Researchers in California enrolled 120 children and adults (age range, 7–55) with peanut allergies to test the long-term effectiveness of peanut OIT.

Patients were randomized to one of three groups:

- Build-up dosing to achieve 4000 mg of peanut powder (\approx 14 peanuts) daily for 2 years, then switch to placebo (oat flour) daily for 1 additional year
- Build-up dosing to achieve 4000 mg of peanut powder daily for 2 years, then switch to 300 mg of peanut powder (\approx 1 peanut) daily for 1 additional year
- Placebo for 3 years

In the two active groups, 85% of patients passed a 4000-mg oral challenge at 2 years, compared with just 4% of control patients. However, during the months after stopping OIT, most patients gradually lost their ability to consume large amounts of peanut protein.

COMMENT: On September 13, 2019, an FDA advisory committee recommended approval of a peanut OIT. If this OIT is approved, peanut-allergic patients will have to make a difficult decision, because a recent meta-analysis showed that patients who are receiving OIT actually experience more allergic reactions and have excess risk for eosinophilic esophagitis than do patients who avoid peanuts (*NEJM JW Gen Med Jun 1 2019* and *Lancet* 2019; 393:2222). And now, these findings suggest that patients might have to continue OIT indefinitely to maintain their desensitization.

CITATION(S): Chinthrajah RS et al. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): A large, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2019 Sep 12; [e-pub]. ([https://doi.org/10.1016/S0140-6736\(19\)31793-3](https://doi.org/10.1016/S0140-6736(19)31793-3))

Lancet 2019 Sep 14; 394:919

Can Mild Asthma Be Managed with Only As-Needed Inhaled Steroids Plus a Bronchodilator?

This approach was better at limiting exacerbations than was daily corticosteroid therapy.

Several trials have shown that as-needed therapy with an inhaled corticosteroid (ICS) plus a bronchodilator is at least as effective as daily ICS maintenance therapy for preventing exacerbations in patients with mild asthma. Researchers in New Zealand now have compared these two approaches in an open-label, “real world” study of 885 patients with mild asthma, 70% of whom had been receiving daily ICS therapy.

Patients were randomized either to open-label daily budesonide plus separate as-needed terbutaline or to as-needed budesonide/formoterol in a dry-powder Turbohaler (not available in the U.S.). During 1 year, severe exacerbations that required at least 3 days of oral corticosteroids were 30% less frequent in the as-needed budesonide/formoterol group than in the daily-treatment group (0.119 vs. 0.172 annually). Compared with the daily-treatment group, the as-needed group received roughly half the cumulative dose of ICS. Inhaler adherence was 76%.

COMMENT: Once again, as-needed ICS/bronchodilator therapy appears to be at least as effective as daily ICS maintenance therapy for preventing exacerbations in patients with mild asthma. Editorialists note that in placebo-controlled studies, as-needed ICS/long-acting β -agonist therapy and maintenance therapy are equally effective, whereas in open-label “real world” studies, as-needed therapy is superior. This probably occurs because most patients don't take their ICS maintenance therapy daily but overuse their albuterol; by combining intermittent ICS with their rescue medication, they get anti-inflammatory treatment when they most need it. We discuss this relatively new approach to mild asthma in more detail in a separate *NEJM Journal Watch General Medicine* [Clinical Spotlight](#) feature.

CITATION(S): Hardy J et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): A 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet* 2019 Sep 14; 394:919. ([https://doi.org/10.1016/S0140-6736\(19\)31948-8](https://doi.org/10.1016/S0140-6736(19)31948-8))

Gauthier M and Wenzel SE. As-needed β agonist-inhaled corticosteroid in mild asthma. *Lancet* 2019 Sep 14; 394:897. ([https://doi.org/10.1016/S0140-6736\(19\)31994-4](https://doi.org/10.1016/S0140-6736(19)31994-4))

A New Approach for Treating Patients with Intermittent Mild Asthma

David J. Amrol, MD *International guidelines recommend as-needed inhaled steroids for mild asthma.*

For many years, as-needed albuterol or another short-acting β -agonist (SABA) has been the standard of care for patients with intermittent asthma, with an added daily inhaled corticosteroid (ICS) for patients with mild persistent asthma. The [U.S. National Asthma Education and Prevention Program \(NAEPP\) guideline](#), last updated in 2007, defines intermittent asthma as symptoms that occur at most twice weekly, nighttime symptoms that occur at most twice monthly, normal lung function, ≤ 1 severe exacerbation annually, and no substantial impairment in activities. Patients with mild persistent asthma have less-than-daily symptoms, nighttime symptoms less often than weekly, mild limitation of activities, or ≥ 2 exacerbations annually, along with normal lung function.

Studies have shown that even patients with intermittent asthma can have severe or fatal exacerbations and that ICS can prevent them. In addition, patients who receive early ICS treatment might retain better lung function and require less ICS later. Given these observations, recent studies have been designed to evaluate as-needed ICS in patients with intermittent or mild persistent asthma. Five randomized trials have confirmed that as-needed ICS combined with a bronchodilator (4 with budesonide/formoterol and 1 with beclomethasone/albuterol) are noninferior to daily ICS for preventing exacerbations in patients with mild asthma (at the expense of a small increase in daily symptom scores). The most recent study was a “real world” open-label trial of as-needed budesonide/formoterol versus daily ICS. It showed that as-needed treatment yielded similar symptom scores and was superior at preventing exacerbations ([NEJM JW Gen Med Oct 15 2019](#) and [Lancet 2019; 394:919](#)). The well-documented fact that most asthma patients do not use their ICS daily when they are asymptomatic probably explains this outcome.

This new body of evidence has led to a change in the [Global Initiative for Asthma \(GINA\) guideline](#); GINA is an international collaboration comprised largely of European asthma experts. GINA classifies asthma severity based on the level of therapy needed to control symptoms after several months of therapy: The intermittent classification is no longer used, and asthma controlled with as-needed therapy or daily low-dose ICS is defined as “mild.” Preferred therapy for patients with symptoms less often than twice monthly is either (a) as-needed low-dose ICS/formoterol (formoterol is a long-acting β -agonist [LABA] with a quick onset of action) or (b) as-needed ICS whenever as-needed SABA is used. For patients whose symptoms are more frequent (but still not on most days), preferred therapy is daily low-dose ICS plus as-needed SABA or as-needed low-dose ICS/formoterol. For more-symptomatic patients, more-intensive treatment is recommended. Notably, GINA strongly discourages use of as-needed monotherapy with a SABA (e.g., albuterol), even in patients with only mild symptoms — and that is a major departure from typical U.S. practice.

In support of as-needed ICS/formoterol for patients with mild symptoms, GINA notes that as-needed ICS/formoterol prevents more exacerbations than does as-needed SABA alone. Moreover, as-needed budesonide/formoterol is as good as daily ICS in preventing severe asthma exacerbations and exposes patients to substantially less inhaled steroid over time.

Wrap-Up; So what is a U.S. clinician to do with the new GINA guideline, given that the NAEPP guideline is relatively outdated? In my view, the GINA guideline should inform practice, but we must be aware that its approach is not FDA approved, it does not apply to children younger than 12, and the device studied for as-needed budesonide/formoterol is the dry-powder Turbohaler (in the U.S., only the metered-dose inhaler is available). In addition, salmeterol (the LABA in Advair) cannot be used as a relief medication, because its onset of action is slower than that of formoterol. Vilanterol (the LABA in Breo) has quicker onset than salmeterol, and in theory, mometasone/formoterol (Dulera) should perform similarly to budesonide/formoterol, but studies have not been performed with as-needed use of either medication.

AstraZeneca chose to bring the metered-dose inhaler version of budesonide/formoterol to the U.S. instead of the dry-powder Turbohaler version based on marketing decisions, and no U.S. clinical trial is on the horizon for as-needed budesonide/formoterol in a metered-dose inhaler, but we might see a combined beclomethasone/albuterol inhaler in the U.S. eventually. Until then, for my patients with mild intermittent asthma who would fall into step 1 GINA therapy (rare symptoms, normal lung function, and no history of severe exacerbations), I will continue to prescribe as-needed albuterol, because it is much less expensive than budesonide/formoterol (Symbicort) — generic albuterol is about US\$50 versus \$300 for a canister of Symbicort. For patients who require step 2 therapy with GINA or for patients with mild persistent asthma based on the older NAEPP guidelines, I have detailed discussions with patients regarding risks and benefits of a daily ICS plus as-needed albuterol versus as-needed ICS/formoterol. More and more often, I end up prescribing as-needed budesonide/formoterol based on patient preference, and I have had very good patient feedback so far.

Do Admission and Readmission Reduction Programs Truly Prevent Hospital Visits?

Admissions are down, but observation stays and emergency department visits are up.

Hospital readmission rates have declined for patients with medical conditions targeted by the Hospital Readmissions Reduction Program (HRRP), established in 2010. In addition, hospitalizations related to ambulatory care–sensitive conditions (ACSCs), such as dehydration, gastroenteritis, and urinary tract infections, which are avoidable if patients have access to high-quality primary care, have also fallen. But do these reductions affect total hospital visits?

In a retrospective cohort study of >3 million index Medicare hospital stays from 2012 through 2015 for heart failure, acute myocardial infarction, or pneumonia, rates of hospital revisits within 30 days after discharge increased steadily. This increase was due to emergency department visits and hospital observations stays — not considered to be hospital admissions, even though patients often do occupy inpatient hospital beds. This increase was offset only partially by declines in readmissions.

In a second study, researchers reviewed a random sample of 20% of all Medicare inpatient and outpatient claims from 2011 through 2015. They found that 75% of the national decrease in avoidable hospitalizations was offset by increases in observation hospital stays.

COMMENT

In the U.S., nationwide reductions in inpatient admission rates for patients with ACSCs and readmission rates for medical conditions targeted by HRRP have been viewed as markers of quality improvement. However, these two studies suggest total hospital revisits are rising. The outcome measures for both programs might need to be reexamined, because emergency and observation stays might simply represent shifts in the site of medical care, substituting for readmissions and ACSC admissions.

CITATION(S): Wadhera RK et al. Hospital revisits within 30 days after discharge for medical conditions targeted by the Hospital Readmissions Reduction Program in the United States: National retrospective analysis. *BMJ* 2019 Aug 12; 366:l4563. (<https://doi.org/10.1136/bmj.l4563>)

Figuerola JF et al. Trends in hospitalization vs observation stay for ambulatory care–sensitive conditions. *JAMA Intern Med* 2019 Aug 26; [e-pub]. (<https://doi.org/10.1001/jamainternmed.2019.3177>)
