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Fewer Patients with Breast Cancer Require Chemotherapy

Outcomes were noninferior with endocrine therapy alone versus chemo-endocrine therapy in patients with intermediate recurrence scores.
Efforts to deescalate the use of chemotherapy in early-stage breast cancer have been ongoing for the last decade, as molecular assays began to be used in clinical decision making. One of the most common prognostic tools in clinical practice is the 21-gene recurrence score (RS; Oncotype DX). Since it was introduced a decade ago for ER+/HER2−, node-negative breast cancer, fewer patients are receiving adjuvant chemotherapy and instead are being treated with endocrine therapy alone. Although RS results at the extremes offer clinicians clarity regarding treatment — chemo-endocrine therapy for high scores and endocrine therapy alone for low scores — intermediate RS results do not help determine the optimal adjuvant therapy.

To address this issue, investigators conducted a randomized phase III trial (TAILORx), in which 6711 women with ER+/HER2−, node-negative breast cancer and intermediate RS results were assigned to chemo-endocrine therapy or endocrine therapy alone. For this study, the intermediate RS range was conservatively defined as 11 to 25, whereas it was originally defined as 18 to 30.

At 9 years, invasive disease-free survival (the primary endpoint) was noninferior with endocrine therapy alone versus chemo-endocrine therapy (83.3% and 84.3%, respectively), as were overall survival (93.9% and 93.8%) and rates of freedom from recurrence at distant sites (94.5% and 95.0%) and local/regional sites (92.2% and 92.9%). An exploratory analysis showed that chemotherapy may offer some benefit in women ≤50 years of age with an RS of 16 to 25.

COMMENT: The finding that most women with ER+/HER2−, node-negative disease can safely avoid chemotherapy is welcome news, and it raises the issue of whether some of these women may benefit from more-aggressive endocrine therapy, including ovarian suppression. Other questions remain, particularly the extent to which younger patients and those with RS of 26 to 30 may derive benefit from chemotherapy.


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BMJ 2018 Mar 7; 360:k671

Plasma 25-Hydroxyvitamin D Concentration Is Associated Inversely with Risk for Cancer

In a prospective observation study, cancer incidence was higher during 17 years in people with low 25(OH)D levels.

Whether plasma 25-hydroxyvitamin D (25(OH)D) concentration is associated with cancer risk is unclear. In this Japanese observational study, investigators assessed the relation between baseline plasma 25(OH)D concentration and subsequent risks for cancer among nearly 34,000 participants in a population-based health study. From this group, 3300 participants with incident cancer were identified during median follow-up of 17 years.

Mean plasma 25(OH)D levels ranged from 14 ng/mL (36 mmol/L) in the lowest quartile to 30 ng/mL (76 mmol/L) in the highest. After adjustment for multiple variables, participants in each of the second-, third-, and fourth-highest quartiles had roughly 20% lower risk for any cancer than did participants in the lowest quartile. The only specific cancer to follow this trend with statistical significance was liver cancer.

COMMENT: In this study, baseline plasma 25(OH)D concentration was associated inversely with risks for total cancer. The authors conclude that “results support the hypothesis that vitamin D might have beneficial effects for cancer prevention.” However, a recent randomized trial showed no benefit of vitamin D supplementation for preventing cancer over 4 years (NEJM JW Gen Med May 1 2017 and JAMA 2017; 317:1234). How might the results

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of these studies be reconciled? One possible explanation is that the duration of the randomized trial (only 4 years) might not have been long enough to show a benefit. Another possible explanation is that the association between low plasma 25(OH)D and cancer in the current observational trial is not causal; rather, factors that contribute to low plasma 25(OH)D also might contribute to cancer risk.


OB/GYN Group Offers Advice on Caring for Teens, Young Women with Eating Disorders

By Amy Orciari Herman

The American College of Obstetricians and Gynecologists has issued a committee opinion on the gynecologic care of adolescents and young women with eating disorders.

Among the recommendations and conclusions:

- Young females with eating disorders may present with gynecologic issues, such as irregular menses, amenorrhea, pelvic pain, and atrophic vaginitis.
- OB-GYNs should know the signs that call for immediate hospitalization for medical stabilization, including dehydration, electrolyte disturbance, and EKG abnormalities (for the complete list, see Box 2 in the committee opinion linked below).
- Clinicians should not prescribe combination oral contraceptives to treat amenorrhea caused by eating disorders.
- Regaining weight is the best remedy for low bone mineral density caused by eating disorders.

ACOG's statement also outlines the diagnostic criteria for eating disorders and offers the five-question SCOFF screening tool for anorexia and bulimia.

LINK(S): ACOG committee opinion (Free)

Menopause 2018 Jun; 25:596

Management of Genitourinary Syndrome of Menopause in Women with or at High Risk for Breast Cancer

Interdisciplinary guidelines for improving quality of life and sexual satisfaction in women with GSM associated with breast cancer.
**Sponsoring Organizations:** The North American Menopause Society and the International Society for the Study of Women's Sexual Health

**Target Population:** Women's health care providers

**Background and Objective:** Despite the high prevalence of genitourinary syndrome of menopause (GSM) among women with or at high risk for breast cancer, information is sparse regarding treatment to improve quality of life and sexual satisfaction. These consensus recommendations were developed by a panel of experts in menopause, sexual health, and oncology.

**Key Recommendations**

- Sexual function and quality of life should be assessed in all breast cancer survivors and those at high risk for breast cancer.
- Management of GSM should be individualized based on shared decision-making involving the patient and her oncologist.
- Initial and mainstay treatment options include vaginal moisturizers and lubricants, vaginal dilators, and pelvic floor physical therapy.
- Although laser therapy may be considered for women requiring or preferring nonhormonal approaches, long-term safety and efficacy data are lacking.
- Low-dose local estrogen therapy may be appropriate for women who have relatively low risk for recurrence, have hormone–receptor-negative disease, are using tamoxifen rather than an aromatase inhibitor, and are particularly concerned about quality of life.
- Observational data suggest that local or systemic hormone therapy do not further increase risk for breast cancer in women already at high risk.
- In women with triple-negative breast cancers, despite a lack of evidence, theoretically there should be no increased risk associated with local or systemic hormone therapy.
- Women with estrogen–receptor-positive disease and failure of nonhormonal therapy may be candidates for local hormone therapy after discussion with an oncologist (women receiving aromatase inhibitors might first consider switching to tamoxifen).
- Compounded hormonal preparations for local therapy are not recommended given their variability and lack of FDA regulation and monitoring.
- In women with metastatic disease, quality of life, comfort, and sexual intimacy are most important when considering potential therapies; optimal choices will vary with probability of long-term survival.

**COMMENT:** These guidelines are largely based on multidisciplinary experts' views, as so little research data exist — but the recommendations do provide a sensible approach to improving quality of life in women with or at substantial risk for breast cancer. Too often, clinicians focus on treating the primary illness without considering the overall wellbeing of the individual. Additional research to further define the safety and efficacy of low-dose local hormone therapy is clearly indicated. Not all practitioners will agree with these guidelines, so it behooves women's healthcare providers to place a high value on sexual health and quality of life when caring for these patients.

Use of Sports Drinks by Adolescents

Most adolescents consume sports drinks weekly, although daily consumption has declined.

Sports drinks are advertised to restore energy and fluids after vigorous exercise. However, the American Academy of Pediatrics (AAP) has concluded that most adolescents need replenishment only with water. Researchers examined data from two large, nationally representative surveys of high school students to identify changes in sports drink consumption over a 5-year period and associations with sociodemographic and lifestyle factors.

Between 2010 and 2015, the proportion of adolescents who consumed sports drinks during the previous week increased slightly but significantly (56.0% to 57.6%), while the proportion consuming sports drinks daily decreased significantly (16.1% to 13.8%). The greatest reductions were among non-Hispanic African-Americans and overweight adolescents. Daily consumption did not decrease in obese adolescents, increased in adolescents who watched more than 2 hours of TV daily, and was twice as likely in boys than girls (18.7% vs. 8.8%).

COMMENT: These trends are eye-opening, as these drinks are designed specifically for athletes and not for sedentary individuals. The increase in overall consumption might reflect an access issue, with teenagers having less access to soda now that vending machines are banned from schools. The increased consumption among youth who view TV excessively suggests that this group may be the most vulnerable to targeted marketing. These beverages are falsely advertised to promote exceptional sports performance and health. Healthcare providers should dispel these myths, inform families about the hidden sugar and calories in these products, and continue to encourage hydration with water alone, as the AAP advocates.

Dr. Gordon is Director, Division of Adolescent and Transition Medicine and Rauh Chair of Adolescent Medicine at Cincinnati Children's Hospital Medical Center, and Professor, Department of Pediatrics, University of Cincinnati College of Medicine.


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Clin Gastroenterol Hepatol 2018 May 8

Consumption of Sweetened Beverages Is Not Associated with Inflammatory Bowel Disease

Prospective, population-based study data refute prior findings.

Findings of a recent meta-analysis as well as a large, ongoing European cohort study show an association between heavier consumption of sweetened beverages and increased risk for developing ulcerative colitis. To examine that association further, investigators analyzed food frequency questionnaire data and incidence of inflammatory bowel disease (IBD) among 83,000 participants enrolled in either the Swedish Mammography Study or the Cohort of Swedish Men — both large, prospective cohort studies.
From 1997 to 2014, there were 143 incident cases of Crohn disease and 349 of ulcerative colitis. Higher consumption of sweetened beverages was not associated with increased risk for Crohn disease or ulcerative colitis. These associations were not modified by age, sex, body-mass index, or smoking, nor when low fiber intake was considered from diet history.

**COMMENT:** The cause of inflammatory bowel disease remains elusive and, given the increasing rates around the world, epidemiologic studies have become even more important to help understand possible underlying pathophysiology. Diet remains a popular target for explaining many conditions, but in these two large populations followed over time, sweetened beverages are not shown to be a causative factor.

Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.


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**Weight Reduction in Childhood Associated with Reduced Risk for Type 2 Diabetes.**

* A heightened risk for type 2 diabetes in adulthood was eliminated in overweight boys who achieved a normal weight by puberty and sustained it into early adulthood.

To determine whether the risk for type 2 diabetes mellitus (DM) in adulthood can be mitigated by weight reduction in overweight and obese children, researchers examined type 2 DM incidence at ages 30 to 60 years in a longitudinal study of 62,000 Danish men from boyhood. Evaluations occurred at age 7 years, at 13 years, and as young adults (ages 17–26). Results were as follows:

- Eleven percent of men developed type 2 DM over nearly 2 million person-years of follow-up.
- The prevalence of overweight was 5% at age 7 years, increasing to 8% in young adulthood.
- While overweight at any age was associated with elevated risk for later type 2 DM, overweight as a young adult conferred the highest risk.
- Boys who were overweight at age 7 years but had normal weight by age 13 years and thereafter were at no greater risk for type 2 DM compared with men who were never overweight.
- Men who were overweight at age 13 years and as young adults had a greater risk for type 2 DM compared with men who were overweight only as young adults.
Among some 500 boys who were obese at age 7 years, 33% remained obese in early adulthood; reducing their body-mass index (BMI) to overweight or normal levels by early adulthood was associated with significant reductions in their future risk for type 2 DM.

Men who were obese in early adulthood had high risk for type 2 DM regardless of their BMI during childhood.

COMMENT: These data provide a glimmer of hope. Boys who are overweight and obese can reduce their risk for type 2 DM with sustained weight reduction. Now we need to find effective ways to help overweight and obese children and adolescents accomplish weight reduction.


Drug Alcohol Depend 2018 May 10

Exposure to Medical Marijuana Ads Is Associated with Increased Use by Adolescents

Youth with increased exposure also reported more negative consequences from use.

Investigators previously showed that exposure to medical marijuana ads is linked to increased past-month marijuana use among adolescents (NEJM JW Pediatr Adolesc Medicine Sep 2015 and Psychol Addict Behav 2015; 29:613). Now they report follow-up data extending an additional 5 years. Sixth- and seventh-graders (ages 11–12 in 2008) from 16 California middle schools were surveyed nine times until 2017 (age 19). Questions included past-week exposure to medical marijuana ads (“not at all” to “every day”), past-month marijuana use, intentions to use, positive expectancies (e.g., “marijuana helps me relax”) and negative consequences (e.g., “got in trouble at school or home”).

Almost 5000 students completed wave 4 surveys (year 2010) and 2500 completed waves 6–9. Analyses controlling for age, race/ethnicity, gender, and participation in a middle school alcohol prevention program demonstrated the following:

- Greater than average ad exposure correlated significantly with greater than average marijuana use, intention to use, positive expectancies, and negative consequences.
- Greater increases in ad exposure were significantly correlated with greater rates of change for all four outcomes, with the strongest correlation between ad exposure and marijuana use.
- Youth reporting higher levels of marijuana use, positive expectancies, and intentions to use had greater subsequent increases in these measures compared with youth reporting lower levels.

COMMENT: Over time, exposure to medical marijuana ads is associated with increased use, intentions to use, positive expectancies about use, and negative consequences. The effects are most pronounced among youth scoring higher than average on three of the four outcomes. Jurisdictions where medical marijuana is legalized should develop regulations that restrict medical marijuana ads targeted towards young people — similar to limits placed on alcohol.

CITATION(S): D'Amico EJ et al. Planting the seed for marijuana use: Changes in exposure to medical marijuana advertising and subsequent adolescent marijuana use, cognitions, and consequences over seven years. Drug Alcohol Depend 2018 May 10; [e-pub]. (https://doi.org/10.1016/j.drugalcdep.2018.03.031)
A Novel Prognostic Tool in Colon Cancer

**Immunoscore had superior prognostic value for overall survival compared with TNM or dMMR status.**

Prognosis in colon cancer is traditionally determined using the TNM (tumor, node, metastasis) classification system. However, scoring tumor-infiltrating T cells is emerging as a novel prognostic measure.

Now, investigators have conducted an industry-supported, international study to evaluate the prognostic value of a consensus Immunoscore in stage I–III colon cancer (Immunoscore–Colon; HalioDx, France). Of 3539 patient samples processed, 2681 were included in the analysis and used as a training set and as internal and external validation sets. The majority of samples were T3 (66.2%), N0 (70.3%), and stage II (53.5%); 11.3% were DNA mismatch repair (dMMR) deficient. Total T-lymphocyte and cytotoxic T-lymphocyte tumor infiltrates were determined using a standardized Immunoscore assay to quantify CD3+ and CD8+ T-cell effectors in submitted tissue blocks. An intermediate Immunoscore was seen in 47.4%, a high score in 26.4%, and a low score in 26.2%.

At a median follow-up of 96 months, a high Immunoscore correlated with lowest risk for recurrence in all study sets. Disease-free survival (DFS) was superior with a high-versus-low Immunoscore (hazard ratio, 0.31; P<0.0001), an intermediate-versus-low Immunoscore (HR, 0.57; P<0.0001), and a high-versus-intermediate Immunoscore (HR, 0.56; P<0.0001). A high-versus-low Immunoscore also correlated with superior DFS in dMMR-deficient patients (HR, 0.56; P<0.0150). Immunoscore had superior and independent prognostic value for overall survival compared with TNM or dMMR status.

**COMMENT:** This ambitious study indicates that Immunoscore may have independent prognostic value in stage I–III colon cancer. Unanswered questions, however, are whether Immunoscore has predictive value to indicate presence or absence of benefit from adjuvant therapy and whether the technology is cost effective and feasible to be routinely applied in clinical practice.


Managing Alopecia Caused by Adjuvant Endocrine Therapy for Breast Cancer

**Topical minoxidil was effective in patients with hair loss caused by tamoxifen or aromatase inhibitors.**

Alopecia caused by adjuvant endocrine therapy is common but has not been as well characterized as that associated with chemotherapy. In a retrospective cohort study at a single U.S. cancer hospital, investigators identified 112 women with alopecia who had received adjuvant endocrine therapy (tamoxifen or aromatase inhibitors [AIs]), but not
chemotherapy, for breast cancer (median age, 60; 76% white, 9% Asian, 6% black). The efficacy of topical 5% minoxidil was assessed with photographs of the scalp taken at baseline and 3 or 6 months. Alopecia resulted from AIs or tamoxifen in 67% and 33% of participants, respectively. The pattern of hair loss resembled androgenic alopecia (increased shedding, with the affected follicles producing shorter, finer, sparse hairs). Based on a validated instrument designed to assess the impact of alopecia, this condition was found to negatively affect women's quality of life (QoL), particularly in the emotional domain. Use of topical minoxidil resulted in moderate or significant improvement in 80% of those who received this treatment.

**COMMENT:** While confirming alopecia's well-known negative emotional impact in breast cancer survivors who received adjuvant endocrine therapy, this study also provides upbeat observations regarding minoxidil's efficacy in managing the condition.


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**BMJ 2018 May 16; 361:k1675**

**Exercise Training Doesn't Slow Progression of Cognitive Decline in People with Dementia**

*Supervised exercise might improve physical fitness but doesn't help cognition.*

Evidence is mixed on whether physical exercise improves cognitive impairment. In this trial, U.K. investigators determined the effects of a moderate-to-high intensity aerobic and strength exercise training program on cognition and other outcomes in 494 people (mean age, 77) with mild-to-moderate dementia.

A total of 329 patients were assigned to an aerobic and strength exercise program, and 165 were assigned to usual care only. The intervention group received 60- to 90-minute, physical therapist–supervised exercise sessions twice weekly for 4 months, followed by prescriptions for unsupervised exercise. Both groups received counseling and advice regarding physical activity. After 12 months, mean scores on a standardized Alzheimer disease cognitive scale were no better in the exercise group than in the usual-care group. Additionally, no differences were found between the groups for secondary outcomes (e.g., activities of daily living, neuropsychiatric symptoms, quality of life) or in subgroup analyses (e.g., by dementia type or severity of cognitive impairment).

**COMMENT:** moderate-to-high intensity exercise training program didn't improve cognition in people with mild-to-moderate dementia. Although formal exercise programs shouldn't be prescribed for this purpose, they might have other physical-fitness benefits that were not captured in this study, for such patients.

**CITATION(S):** Lamb SE et al. Dementia and Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: Randomised controlled trial. BMJ 2018 May 16; 361:k1675. (https://doi.org/10.1136/bmj.k1675)
Cleavage of amyloid precursor protein by beta-site amyloid precursor protein-cleaving enzyme 1 (BACE-1) leads to amyloid-beta (Aβ) production in Alzheimer disease (AD). To investigate the safety and efficacy of verubecestat, an investigational oral BACE-1 inhibitor, researchers conducted a randomized, double-blind, placebo-controlled, manufacturer-funded, phase III clinical trial. Participants were randomized to 12 mg verubecestat (n=653), 40 mg verubecestat (n=652), or placebo (n=653) daily for 78 weeks. Primary outcomes included scores on the ADAS-Cog and the ADCS-ADL scales. AD biomarker measurements included cerebrospinal fluid (CSF) tau and amyloid-beta levels and amyloid load based on positron emission tomography imaging. At baseline, mean age was 71 to 72 years, Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) scores were about 21 points and Alzheimer's Disease Co-operative Study–Activities of Daily Living Inventory (ADCS-ADL) scores were about 63 points for all groups, and approximately 90% had biomarker findings suggestive of AD pathology.

The study was stopped early due to futility of treatment. From baseline to week 78, the mean change in scores was ~8 points for the ADAS-Cog and between −8.2 and −8.9 points for the ADCS-ADL in all groups. Amyloid load decreased from baseline to week 78 in the verubecestat groups. There were no significant changes in CSF total tau, but verubecestat was associated with increased CSF Aβ 42 levels from baseline to 78 weeks. More adverse effects were seen with verubecestat, including rashes, falls, sleep issues, suicidal ideation, weight loss, and change in hair color.

**COMMENT:** Although verubecestat is not effective in mild-to-moderate AD, treatment timing may have contributed to the results. Another trial is investigating whether BACE-1 inhibition may be effective in those at risk for AD during the pre-symptomatic disease stages, when amyloid plaque formation is more prominent (NCT02569398; ClinicalTrials.gov).

Intimate Partner Violence Can Take Many Forms

Like physical, sexual, and emotional violence, economic violence might strongly contribute to depression and suicidal ideation in women.

Intimate partner violence (IPV) is ordinarily defined as violence or abuse that is physical, sexual, or emotional/psychological. Researchers in South Africa examined how these IPV types, along with economic IPV, might affect mental health.

In a community-based study, 680 women (mean age, 24) living in impoverished areas, completed a series of structured questionnaires assessing depression, suicidal ideation, and frequency of IPV. Close to half of the women scored in the clinically relevant range for past-week depression; almost one third reported suicidal ideation in the previous month. Sizable percentages of women reported ≥2 episodes of each type of IPV in the previous year:

- Emotional IPV (insults, humiliation; threats to harm, scaring, hurting others of importance), 67%
- Economic IPV (preventing a woman from earning money, taking her money, throwing her out of the home, spending money needed for the household on alcohol, tobacco, or self), 44%
- Physical IPV, 49%
- Sexual IPV, 21%

Depression and suicidal ideation scores were highest among women reporting all four types of IPV. However, these scores were higher among women experiencing only emotional IPV, economic IPV, or both than among those reporting only physical IPV, sexual IPV, or both. Suicidal ideation was more strongly tied to economic IPV than emotional IPV.

COMMENT: In this impoverished population, the high prevalence of each IPV type and the strong association of IPV types to clinically relevant depression and suicidal ideation are notable. Data from poverty-stricken areas and highly distressed populations in the U.S. suggest similar associations. This study highlights the multiple faces of IPV, the strong psychological impact of economic stressors, and the importance of conducting “psycho-economic” assessments in routine clinical practice.