11-10-18

Helicobacter 2018 Oct; 23:e12532

Does Eating Garlic Decrease Gastric Cancer Risk?

High garlic consumption conferred a 50% reduction in gastric cancer risk in a meta-analysis, but study limitations prevent any definitive conclusions.

Garlic is in the Allium (onion) family, which is associated with many putative health benefits, including improved blood pressure, reduced cholesterol, and decreased gastric cancer risk. One hypothesis for the possible decrease in gastric cancer risk is suppression of *Helicobacter pylori* by garlic. Although there have been many studies investigating the association of garlic with a gastric cancer risk, no firm conclusions can be made from those individual studies.

In a meta-analysis of data from 18 studies comprising 143,000 participants, the highest garlic consumption compared with the lowest was significantly associated with a 50% reduced risk for gastric cancer. Eating garlic at least once daily was associated with a 35% decreased risk for gastric cancer. When the analysis was restricted to only prospective studies (1 randomized controlled trial and 2 cohort studies), pooled risk reduction estimates were not significant. Importantly, risk for bias was high in the nonrandomized studies, particularly biases introduced via patient selection, confounding, and classification of interventions.

COMMENT: Despite this positive meta-analysis finding of an inverse association of garlic intake and gastric cancer, the analyzed studies have significant limitations. Thus, we cannot conclude any significant benefit of garlic in this setting. I suggest that if you enjoy the distinctive taste of garlic, tolerate it without adverse gastrointestinal symptoms, and those around you do not mind it, continue to consume it. However, the data do not support recommending garlic consumption to patients for prevention of gastric cancer.

CITATION(S): Li Z et al. The association of garlic with *Helicobacter pylori* infection and gastric cancer risk: A systematic review and meta-analysis. Helicobacter 2018 Oct; 23:e12532. (http://dx.doi.org/10.1111/hel.12532)

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JAMA Neurol 2018 Oct 15

To Protect the Brain, Look to the Ovaries

Imaging study suggests surgical menopause leads to temporal lobe degeneration that may precede dementia.

Bilateral salpingo-oophorectomy (BSO) prior to menopause is well known to increase risk for cognitive impairment — including dementia. To explore the neuronal basis of this deterioration, investigators in Minnesota performed a population-based cohort study involving women who had undergone BSO from 1988 through 2007 (median age at BSO, 46) compared with those who had not undergone such surgery (control). All 43 participants underwent neuropsychological evaluation as well as magnetic resonance imaging and positron emission tomography (median age at imaging, 63).

The amygdala was smaller ($P<0.001$), the parahippocampal-entorhinal cortex was thinner ($P=0.046$), and entorhinal white matter fractional anisotropy (an index of neuronal connectivity) was lower in the BSO group ($P=0.030$). Menopausal hormone therapy (HT) was used for a median 10 years by 96% and 53% of the BSO and control groups, respectively. Conventional tests of cognitive function yielded similar results in both groups.

COMMENT: This small cohort study indicates that the abrupt declines in brain exposure to ovarian steroids associated with surgical menopause may in turn produce deleterious structural changes in the medial temporal lobe. As earlier work indicated that estrogen therapy can protect against cognitive decline associated with premenopausal BSO (NEJM JW Womens Health Dec 2007 and *Neurology* 2007; 69:1074), it's somewhat surprising that HT did not prevent the neuroanatomic changes observed here. Ongoing follow-up will help determine if these neuroanatomic changes trigger clinically important cognitive changes later in life.

CITATION(S): Zeydan B et al. Association of bilateral salpingo-oophorectomy before menopause onset with medial temporal lobe neurodegeneration. JAMA Neurol 2018 Oct 15; [e-pub]. (https://doi.org/10.1001/jamaneurol.2018.3057)

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JAMA Intern Med 2018 Oct 1

Does Drinking Additional Water Prevent Recurrent UTI?

That depends on baseline intake.

Recurrent urinary tract infection (UTI) in premenopausal women causes substantial morbidity and raises concerns about antimicrobial resistance associated with repeated courses of antibiotics. To test whether additional hydration lowers risk for recurrent UTI, investigators in Bulgaria randomized 140 women with ≥3 episodes of cystitis during the past year who reported drinking <1.5 L fluid daily to receive an additional 1.5 L of water daily (water group) or no additional fluid (control group).

At 1-year follow up, mean number of cystitis episodes was 1.7 in the water group versus 3.2 in the control group and mean number of antibiotic courses was 1.9 in the water group versus 3.6 in the control group ($P<0.001$ for both comparisons).

COMMENT: This study offers rigorous proof of a simple idea that drinking more water — when preexisting intake is less than recommended — substantially lowers risk for recurrent UTI. Given that frequently recurrent UTI represents a vexing problem for affected women, it's likely that these findings can be translated into a strong recommendation to increase fluid intake. However, whether drinking more fluid can also benefit women who already have adequate intake remains unknown.

CITATION(S): Hooton TM et al. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: A randomized clinical trial. JAMA Intern Med 2018 Oct 1; [e-pub]. (https://doi.org/10.1001/jamainternmed.2018.4204)

Grady D. Drinking more water for prevention of recurrent cystitis. JAMA Intern Med 2018 Oct 1; [e-pub]. (https://doi.org/10.1001/jamainternmed.2018.4195)

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Gastroenterology 2018 Oct 17; S0016-5085(18)35159-X

Mortality Risk in Childhood-Onset Inflammatory Bowel Disease

Population-based data show a threefold elevated risk for all-cause death compared with healthy, matched children.

Some data indicate that patients with inflammatory bowel disease (IBD) have an elevated risk for death from all causes as well as certain cancers. However, data in patients whose IBD is diagnosed during childhood are lacking.

Using the Swedish National Patient Registry data, investigators identified 9442 incident cases of IBD diagnosed in patients under age 18 years from 1964 through 2014. Based on 139,000 person-years of follow-up, results were as follows:

- There were 259 deaths among people with IBD (133 were from cancer and 54 from digestive disease).
- The all-cause mortality rate in these patients was 2.1/1000 person-years, compared with 0.7 in matched reference individuals from the general population.
- The average age at death was 61.7 compared with 63.9 years in the reference group.
- The hazard ratio for death was 3.2 and was higher in those with ulcerative colitis (HR, 4.0), especially if they had concomitant primary sclerosing cholangitis (HR, 12.2), a first-degree relative with ulcerative colitis (HR, 8.3), or a history of surgery (HR, 4.6).
- Mortality risks were similar when limited to the period after the introduction of biologics (2002–2014).

COMMENT: Chronic inflammation and chronic immune suppression each contribute in their own way to increasing mortality. In IBD, long-term steroid use and narcotics use have both been shown to increase mortality despite our advances in effective therapies. Despite this study's strong population-based design, the absolute numbers are small, so it is hard to make any hard-and-fast conclusions. However, the takeaway for clinicians is the importance of minimizing inflammation, but also immune suppression, in IBD. For patients, this means engaging in health maintenance and prevention of disease complications to the extent possible, including getting vaccinations.

CITATION(S): Olén O et al. Increased mortality of patients with childhood-onset inflammatory bowel diseases, compared with the general population. Gastroenterology 2018 Oct 17; S0016-5085(18)35159-X; [e-pub]. (https://doi.org/10.1053/j.gastro.2018.10.028)

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Pediatrics 2018 Oct 31

Small Increase in Body-Mass Index Linked to Early Antibiotic Exposure

Any exposure to antibiotics before 2 years of age was associated with a slightly increased risk for overweight or obesity by age 5.

Studies of a possible link between early-life antibiotic exposure and increased weight gain, largely from single centers, have produced mixed evidence.

Using data from 362,550 patients reported by 35 institutions in a clinical research network, researchers examined body-mass index (BMI) z score and risk for overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) at age 5 years by number of antibiotics exposures before age 24 months (0, 1, 2, 3, ≥4). Covariates included corticosteroid episodes, number of encounters, and number of infections before 24 months, as well as sex, race, ethnicity, preterm birth, and asthma. Analyses were done separately for children with versus without a chronic complex condition.

At 5 years of age, 28% of children were overweight or obese. Among children with no chronic complex condition, receiving any antibiotics (vs. none) before age 24 months was associated with a higher BMI z score (+0.04) and increased odds of overweight or obesity (odds ratio, 1.05; 95% confidence interval, 1.00–1.07). A dose-response relationship was observed for both outcomes. Results were similar, though of slightly greater magnitude, for children with a complex chronic condition and for broad-spectrum versus narrow-spectrum antibiotics. The number of infections before age 24 months also was related to increased BMI, attenuating the relationship between antibiotics and overweight/obesity.

COMMENT: These results support a link between early antibiotic use and increased BMI, but the effect appears small enough to be clinically unimportant to individual children. Antibiotic effects on the microbiome and the relationship of infections to obesity continue to be investigated. From this and similar studies, the take-home message for the clinician is that the side effects of early antibiotic use do not appear to include significant risk for later overweight or obesity.

CITATION(S): Block JP et al. Early antibiotic exposure and weight outcomes in young children. Pediatrics 2018 Oct 31; [e-pub]. (https://doi.org/10.1542/peds.2018-0290)

Saari A and Sankilampi U. Is there a causal link between antibiotic exposure during infancy and risk for obesity? Pediatrics 2018 Oct 31; [e-pub]. (https://doi.org/10.1542/peds.2018-2692)

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JAMA Pediatr 2018 Oct 22

Can Docosahexaenoic Acid Supplementation Help Toddlers Born Preterm?

DHA did not improve development in toddlers born at less than 35 weeks' gestation.

Docosahexaenoic acid (DHA) is an omega-3 fatty acid with multiple roles in development, including brain structure and function. Preterm infants are born deficient in DHA and may benefit from supplementation, but the optimal timing of supplementation is unknown.

Researchers randomized 377 infants (10−16 months corrected age) born at less than 35 weeks' gestation to receive either DHA and arachidonic acid (DHA+AA, 200 mg each) or placebo (corn oil) daily for 6 months. Developmental progress, measured at 16 to 22 months corrected age using the cognitive composite of the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III), was compared between groups. Secondary outcomes related to language and motor development, effortful control, and activity were measured using the Bayley-III and two developmental questionnaires completed by parents.

Developmental outcomes did not differ between the groups, except in two subgroups of toddlers. In lower-birth-weight toddlers, DHA+AA supplementation was associated with moderate negative effects on language and, in toddlers from families with annual income >$35,000, a similar negative effect on effortful control was associated with supplementation.

COMMENT: Because of its known role in brain development, DHA has become a popular supplement for infants and toddlers, but evidence from high-quality studies has been lacking. This study adds important information, suggesting that supplementation with DHA and AA does not improve ex-preterm toddlers' cognitive or behavioral development. Clinicians can help families navigate supplementation fads by sharing the evidence from well-designed studies and discussing the problems with observational and cross-sectional findings used by companies to promote little-regulated products directly to parents.

CITATION(S): Keim SA et al. Effect of docosahexaenoic acid supplementation vs placebo on developmental outcomes of toddlers born preterm: A randomized clinical trial. JAMA Pediatr 2018 Oct 22; [e-pub]. (https://doi.org/10.1001/jamapediatrics.2018.3082)

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Court Rules Pharmacy Benefit Managers Must Face Lawsuit Over EpiPen Price Hikes

ASHP Daily Briefing; Tuesday, October 30, 2018

A federal judge in St. Paul, Minnesota has ruled that four pharmacy benefit managers "must face a lawsuit alleging they breached their duties as administrators of employee health-insurance plans' drug benefits by causing Mylan NV to raise the EpiPen allergy medication's price." The companies had asked the court to dismiss the class action claims against them.
ASHP Daily Briefing; Tuesday, October 30, 2018

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Radiotherapy Patients Can Safely Use Lotions for Irritated Skin

https://www.medscape.com/viewarticle/904063

For years, radiation oncologists have been telling patients to avoid applying topical creams, lotions, or emollients immediately before radiation treatment. That instruction was based on a concern that applying creams could increase the risk for, or worsen, radiation dermatitis or that it would increase the intensity of skin toxicity from the radiation.

A new study published online October 18 in *JAMA Oncology* challenges that recommendation. Lead author, Brian C. Baumann, MD, a radiation oncologist from Washington University in St. Louis, Missouri, told *Medscape Medical News*. "But we found that the amount of cream that patients typically apply to their skin was not enough to cause any interference on skin dose," Baumann said.

"This is indeed a good-news study," Chelsea C. Pinnix, MD, PhD, the University of Texas MD Anderson Cancer Center, Houston, who wrote an accompanying editorial, told *Medscape Medical News*. "Some creams that are commonly used have a low metallic content, so the concern was that the metal in the cream may interact with the x-rays and lead to increased dose," she said. But these researchers "found in the paper that most patients apply these lotions moderately, about 2 millimeters or less in thickness, and so radiation dose is not increased at the skin in most clinical situations. This is a pretty simple, straightforward study, but it does have the ability to really impact practice and treatment recommendations that we make to patients, and that may also improve their experience during radiation treatment," she said.
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Obstet Gynecol 2018 Oct; 132:895

When Is the Best Postpartum Time to Place an IUD?

To minimize risk for complete intrauterine device expulsion, place the device either within 10 minutes of delivery or at ≥4 weeks postpartum.

Highly effective reversible contraceptives such as intrauterine devices (IUDs) and subdermal implants are commonly offered and placed at a postpartum visit. However, many women do not adhere to this visit — and some will become pregnant again within 24 months. For these women, placement of an IUD at birth or an implant before hospital discharge will provide long-acting contraception. To synthesize the available information on likelihood of IUD expulsion following postpartum placement, investigators identified 48 studies including some 8000 placements. Timing was categorized as immediate (within 10 minutes of placental delivery), early (>10 minutes to <4 weeks postpartum), or interval (≥4 weeks postpartum).

Interval placement was associated with the lowest rate of complete expulsion (1.9%) and early placement with the highest rate (29.7%); immediate placement had a 10.0% rate of complete expulsion. Among the 14 studies reporting IUD expulsion rates >6 months after birth, complete expulsion rates were 9.2% (immediate), 33% (early), and 3.4% (interval). In analysis by delivery method, expulsion rates after pooled immediate or early placement were 14.9% (vaginal) and 3.6% (cesarean). By IUD type, these pooled expulsion rates were 16% (LNG-IUD) and 7% (CuT380A copper IUD).

COMMENT: This study clearly shows that if an IUD is to be placed during hospitalization for birth, it's best to do so immediately following delivery. This requires the birth center or hospital to have copper and levonorgestrel IUDs available in the delivery room at all times.

CITATION(S): Jatlaoui TC et al. Intrauterine device expulsion after postpartum placement: A systematic review and meta-analysis. Obstet Gynecol 2018 Oct; 132:895. (https://doi.org/10.1097/AOG.0000000000002822)

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Neurology 2018 Oct 23; 91:e1559

Pregnancy Rates in Multiple Sclerosis Increasing Over Time

Women with MS were more likely than other women to have a claim for complication during pregnancy, labor, and delivery.

Researchers retrospectively studied pregnancy rates, complications, and outcomes in women with and without multiple sclerosis (MS) using the 2006 to 2015 IQVIA Real World Data Adjudicated Claims — U.S. database, which represents commercially insured individuals generally younger than 65. The annual number of women with MS included through 2014 ranged from 36,361 to 58,218. Of 2176 patients with MS who had a live birth plus follow-up for at least 1 year pre- and postpregnancy, 2115 women with MS were propensity score matched 1:1 to women without MS for age, region, payer, and comorbidities.

Overall, the mean age of pregnancy was higher for those with MS than for those without MS (32.5 vs. 29.3 years). Over time, the adjusted pregnancy rate flipped from being higher in women without MS (8.8% without vs. 7.9% with in 2006), to higher in women with MS (9.5%, vs. 7.8% without MS in 2014). In the propensity-matched analysis, patients with MS were significantly more likely to have a claim for premature labor (31.4% vs. 27.4%), infection in pregnancy (13.3% vs. 10.9%), maternal cardiovascular disease (3.0% vs. 1.9%), and anemia or acquired coagulation disorder (2.5% vs. 1.3%). There were no differences in rates of diabetes, hemorrhage, preeclampsia, placenta previa, or threat of miscarriage. Patients with MS were more likely to have labor and delivery complications, specifically acquired damage to the fetus (27.8% vs. 23.5%) and congenital fetal malformations (13.2% vs. 10.3%).

COMMENT: Pregnancy rates are increasing over time among women with MS but seem to be at later ages than among women without MS. The increased rate could reflect better counseling, and the later age could reflect medical planning for pregnancy. Several complications were slightly more common in those with MS. Whether this is due to the disease or increased vigilance for those with a chronic illness remains unknown. Close follow-up with the obstetrician is recommended.

CITATION(S): Houtchens MK et al. Pregnancy rates and outcomes in women with and without MS in the United States. Neurology 2018 Oct 23; 91:e1559. (https://doi.org/10.1212/WNL.0000000000006384)

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Neurology 2018 Oct 23; 91:e1570

Multiple Sclerosis Relapses Decline During Pregnancy, Rebound in Puerperium

U.S. claims data suggest a high rate of relapse after delivery and low use of MS therapies in the years before and after pregnancy.

To examine use of disease-modifying drugs for multiple sclerosis (MS) before, during, and after pregnancy, researchers used the 2006 to 2015 IQVIA Real World Data Adjudicated Claims–US database, which is designed to be representative of U.S. commercially insured individuals younger than 65. Inclusion criteria were women with an MS diagnosis code and a pregnancy-related code.

Of 205,466 women with MS, a pregnancy diagnosis claim was entered for 10,630, of whom 2158 had a live birth with 1 year of continuous insurance eligibility prepregnancy and 1 year postpregnancy. Compared with the prepregnancy period, odds of relapse declined to 0.62 during pregnancy, increased to 1.71 in the puerperium (delivery through 6 weeks), and ended higher in the latter part of that year, at 1.22. In the year after birth, 28.5% of women initiated an MS therapy, at a median of 93.5 days. Patients on disease-modifying therapy 1 year prepregnancy were more likely to reinitiate therapy within 1 year after delivery (72.6% on treatment prepregnancy vs. 12.4% not on treatment prepregnancy).

COMMENT: The authors found low use of MS therapies in the year leading up to pregnancy, along with the year following delivery. The reasons for low medication utilization remain unclear; women may have stopped while attempting conception beyond 1 year, or they may have stopped or never started therapy for other reasons. The relapse rates were 2.6% per month in the puerperium period and 1.7% to 2.0% per month from the puerperium period through 1 year postpartum. Whether untreated women were breast-feeding (exclusively or otherwise) was not known. This study demonstrates that women with MS are at high risk for relapse in the year following delivery, and few women restart therapy.

CITATION(S): Houtchens MK et al. Relapses and disease-modifying drug treatment in pregnancy and live birth in US women with MS. Neurology 2018 Oct 23; 91:e1570. (https://doi.org/10.1212/WNL.0000000000006382)

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N Engl J Med 2018 Nov 1; 379:1711

A New Approach to Lymphoma Treatment

Combining rituximab with an anti-CD47 monoclonal antibody led to high response rates in relapsed or refractory B-cell lymphoma.

Overcoming tumor-induced blockade of innate anticancer immunity is increasingly important across cancer subtypes.

Now, investigators report the results of a phase I study in which 15 patients with diffuse large B-cell lymphoma (DLBCL) and 7 patients with relapsed or refractory follicular lymphoma (FL) were treated with the 5F9 monoclonal antibody targeting CD47, a "don't eat me" signal expressed by some lymphomas that blocks macrophage ingestion. Patients received low-dose 5F9 (1 mg/kg) in week 1, followed by weekly 5F9 (10–30 mg/kg) plus rituximab. All patients were heavily pretreated, and 95% were rituximab refractory.

Among DLBCL patients, 40% responded, and 33% had complete responses. Among FL patients, 71% responded, and 43% had complete responses. At a median follow-up of 6 to 8 months, 91% of responses were ongoing. Toxicities were mostly grade 1 or 2, including hemolytic anemia, an expected effect owing to CD47 expression on aged and senescent red blood cells. The low-dose, week-1 5F9 effectively ameliorated hemolysis risk for most patients. A 30-mg/kg therapeutic dose was selected for phase II studies.

COMMENT: This novel mechanism of overcoming immune blockade by masking CD47 and thus allowing phagocytosis of lymphoma cells opsonized by rituximab is highly encouraging. Further development of this strategy will be of great interest, potentially for less-refractory disease or to deepen responses post–induction therapy. Of note, acquired CD47 expression is also observed in some solid tumors, including colorectal, and clinical trials of combining antitumor monoclonal antibodies with anti-CD47 targeting are in progress.

CITATION(S): Advani R et al. CD47 blockade by Hu5F9-G4 and rituximab in non-Hodgkin's lymphoma. N Engl J Med 2018 Nov 1; 379:1711. (https://doi.org/10.1056/NEJMoa1807315)

Mantovani A and Longo DL. Macrophage checkpoint blockade in cancer— Back to the future. N Engl J Med 2018 Nov 1; 379:1777. (https://doi.org/10.1056/NEJMe1811699)

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N Engl J Med 2018 Oct 20

Immunotherapy for Breast Cancer Has Arrived

Adding atezolizumab to nab-paclitaxel prolonged progression-free survival in patients with metastatic triple-negative breast cancer.

The impact of immunotherapy as a component of standard treatment has been felt much more slowly in breast cancer than in other malignancies. Small trials have suggested the potential of checkpoint inhibitors, particularly in triple-negative breast cancer (TNBC), but randomized trials have been lacking.

Now, investigators report the results of an industry-sponsored, randomized, phase III trial (IMpassion130) in which 902 untreated TNBC patients received nab-paclitaxel with or without atezolizumab, a monoclonal antibody that targets PD-L1 and prevents interaction with PD-1 and B7-1, a costimulatory cell surface protein. Through this mechanism, T-cell suppression is reversed, leading to an antitumor effect. Also, taxanes are not only active in TNBC, they also may potentiate the antitumor effect of checkpoint inhibitors such as atezolizumab.

At a median follow-up of 12.9 months, median progression-free survival (PFS; the primary endpoint) was prolonged for patients receiving nab-paclitaxel plus atezolizumab versus nab-paclitaxel plus placebo (7.2 vs. 5.5 months; hazard ratio, 0.80; *P*=0.002). In the subset of patients with PD-L1–positive tumors, median PFS was also prolonged with atezolizumab (7.5 vs. 5.0 months; HR, 0.62; *P*<0.001). Overall survival (OS) was nonsignificantly longer with atezolizumab versus placebo for all patients (21.3 and 17.6 months, respectively). Adverse events were similar between treatment arms, although nausea, cough, neutropenia, fever, and hypothyroidism were more common among those receiving atezolizumab.

COMMENT: The results of this trial will likely lead to a new standard treatment for patients with metastatic TNBC. The improvement in outcome of both PFS and OS, particularly in the PD-L1–positive patients, is clinically meaningful. In this experience, the adverse-effect profile of combining chemotherapy with atezolizumab is predictable and manageable and not significantly worse than with chemotherapy alone.

CITATION(S): Schmid P et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018 Oct 20; [e-pub]. (https://doi.org/10.1056/NEJMoa1809615)

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