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**Does Prophylactic Salpingo-Oophorectomy Also Reduce Risk for Breast Cancer?**

**"Digital Skin" Could Revolutionize New Drug Development**

Tata Consultancy Services (TCS) is currently looking at ways to develop and administer drugs more efficiently, economically, and ethically. The firm has patented a new computer model which it says could not only completely change the way drugs are delivered into the body but reduce the need for animal testing in the years ahead. Called "digital skin," the innovation is designed for both personal care and pharmaceutical companies on how to deliver drugs painlessly through the skin, rather than through tablets, capsules, injections, or other invasive methods.

TCS' digital skin is described as a digital replica of every distinct layer of skin that the firm explains enables researches to explore hundreds of thousands of molecule and drug combinations. Testing using the digital skin is not only more accurate but is better than animal skin because the latter is not the same as human skin. The animal models don't replicate human behavior, which means that, quite often, your drug fails in later stage clinical trials.

https://www.forbes.com/sites/leebelltech/2019/02/27/a-digital-skin-innovation-could-revolutionize-new-drug-development/#f669c8675343
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## More Evidence Backs the Hormone Therapy Timing Hypothesis

*Recency of menopause shaped the relation between plasma estradiol levels and atherosclerotic plaque progression.*

In 2016, the ELITE trial showed that oral estradiol (E2) administered to women <6 years after menopause slowed progression of subclinical atherosclerosis (indicated by carotid intima-media thickness), while having no effect in women who were ≥10 years postmenopause (NEJM JW Womens Health May 2016 and *N Engl J Med* 2016 374:1221). In this secondary analysis, ELITE investigators assessed the effect of plasma E2 levels on progression of subclinical atherosclerosis.

Among 596 participants (70% non-Hispanic white), plasma E2 levels were available in 248 early postmenopausal and 348 late postmenopausal women (mean age, 55 and 64, respectively). E2 levels were inversely associated with atherosclerosis progression in early postmenopausal women but positively associated with progression in late postmenopausal women.

**COMMENT;** These data provide yet further support for the hormone therapy (HT) timing hypothesis, which postulates that HT slows atherosclerotic plaque progression in recently menopausal women but has neutral or adverse effects in women who are at least a decade past menopause. As the authors suggest, the favorable vascular effects of E2 appear limited to those women who have not yet developed atherosclerosis. Whether or not HT should be considered for cardioprotection remains unresolved (and controversial). But these data — along with findings of the Women's Health Initiative — provide reassurance about the cardiovascular safety of HT when prescribed to recently menopausal women with bothersome vasomotor symptoms.

**CITATION(S):** Sriprasert I et al. Differential effect of plasma estradiol on subclinical atherosclerosis progression in early versus late postmenopause. J Clin Endocrinol Metab 2018 Sep 28; [e-pub]. (https://doi.org/10.1210/jc.2018-01600)

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## Breast Cancer After a Baby

*Childbirth seems to raise risk for breast cancer diagnosis before age 55.*

Breast cancer is a common concern among women of reproductive age. To evaluate the

effects of recent childbirth on risk for developing breast cancer before age 55, international researchers pooled individual-level data from 15 prospective cohort studies.

During 9.6 million person-years of follow-up, 18,826 incident breast cancers were diagnosed. Compared with nulliparous women younger than 55, parous women were more likely to be diagnosed with breast cancer up to 24 years after giving birth, particularly if they had family histories of breast cancer, were older at first birth, or gave birth multiple times. Although breast-feeding reduces women's lifetime risk for breast cancer, this practice was not found to modify risk for breast cancer diagnosis before age 55. Similarly, oral contraceptive use was not found to increase risk for breast cancer.

**COMMENT:** This impressive international collaboration expands our understanding of the variable effects of pregnancy and lactation on breast cancer risk. Although alcohol consumption is widely recognized as a modifiable risk factor for breast cancer, this variable was not studied here. In my own practice, I will continue to advise patients interested in lowering their risk for breast cancer to limit alcohol consumption, breast-feed their infants, and — if they have family

histories of breast cancer (and high breast cancer risk assessment scores) — consider recommended prophylactic medications such as tamoxifen.

**CITATION(S):** Nichols HB et al. Breast cancer risk after recent childbirth: A pooled analysis of 15 prospective studies. Ann Intern Med 2018 Dec 11; [e-pub]. (https://doi.org/10.7326/M18-1323)

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J Natl Cancer Inst 2018 Oct 11

## Monitoring Patients with Early-Stage Breast Cancer: Time to Reassess?

*The presence of circulating tumor cells after chemotherapy was prognostic of poor survival; should more active surveillance based on molecular evidence be reconsidered?*

One of the most frequently asked questions by patients with early-stage breast cancer is how will they be followed for evidence of disease recurrence. The current recommendation to follow largely by clinical exam is often met with astonished looks questioning why more isn't done. To date, clinical practice guidelines support this conservative approach, which is based largely on older clinical trials that showed that doing more in the way of imaging or classic tumor markers did not improve outcome. However, in the era of molecular testing and assays that assess circulating tumor cells (CTCs), circulating tumor free DNA, and other potential "fingerprints" of residual tumor cells, the notion of monitoring patients more aggressively is being revisited.

To that end, investigators conducted an industry-funded, prospective, multicenter, randomized, open-label, phase III trial (SUCCESS A) in which CTCs were monitored before and 2 years after chemotherapy in 1087 patients with early-stage breast cancer. Patients were assigned to three cycles of fluorouracil-epirubicin-cyclophosphamide (FEC) followed by three cycles of either docetaxel or docetaxel plus gemcitabine. Once chemotherapy was complete, patients were randomized to 2 or 5 years of zoledronate.

At a follow-up of 37 months, 198 patients (18.2%) were CTC-positive 2 years after chemotherapy. The presence of CTCs 2 years after chemotherapy was an independent prognostic factor for poor overall and disease-free survival, independent of CTC status at baseline. Patients who were CTC-positive at baseline and at the 2-year follow-up had the worst survival prospects. The prognostic power of the presence of CTCs was apparent in all subtypes of breast cancer except HER2-positive cancers.

**COMMENT:** CTCs represent residual disease, and by the results of the current trial, increase the risk for clinical recurrence and, ultimately, shorter survival. Knowing this information does not necessarily imply that we have a therapy or approach that will alter that outcome. Nevertheless, it raises the question as to whether the time is right to launch clinical trials that identify such patients with molecular evidence of residual disease and randomize them to an intervention or standard clinical follow-up. Such trials are now being considered by the cooperative groups.

**CITATION(S):** Trapp E et al. Presence of circulating tumor cells in high-risk early breast cancer during follow-up and prognosis. J Natl Cancer Inst 2018 Oct 11; [e-pub]. (https://doi.org/10.1093/jnci/djy152)

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# Predicting Rebleeding in Patients with Idiopathic Peptic Ulcers

*Using machine-based learning, a predictive score was derived and validated in patients with* Helicobacter pylori–*negative ulcers.*

The major risk factors for peptic ulcers that bleed are *H. pylori* and nonsteroidal anti-inflammatory drugs (NSAIDs). However, idiopathic peptic ulcers, or IPUs, an increasingly prevalent category, have no identified risk factors and are associated with increased risk for further bleeding.

In an analysis of a large, prospectively collected database from Hong Kong, machine learning was used to build a model (called the IPU-ML) to predict IPU rebleeding. The training model, derived from 22,900 patients with IPU, was built on six clinical parameters: age; hemoglobin; and the presence of gastric ulcer, gastrointestinal diseases, malignancies, and infections. It was prospectively validated in 1300 patients with a bleeding IPU, among whom bleeding recurred in 190 patients. In the validation cohort, patients with recurrent IPU bleeding within 1 year were identified with a negative predictive value of 99% and an overall accuracy of 84%.

**COMMENT:** IPUs are difficult to manage, as there are no modifiable risk factors to treat. This study utilizes a large database of peptic ulcers to identify risk factors for recurrent IPU bleeding. The high-risk IPU patients may benefit from potent acid suppression, although I could not determine if some of the patients in this study were already on antiacid therapy. In my clinical practice, I err on the side of providing long-term acid suppression in patients with idiopathic bleeding ulcers given their high rates of rebleeding.

**CITATION(S):** Wong GL-H et al. Machine learning model to predict recurrent ulcer bleeding in patients with history of idiopathic gastroduodenal ulcer bleeding. Aliment Pharmacol Ther 2019 Feb 13; [e-pub]. (https://doi.org/10.1111/apt.15145)

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# Fluconazole and Risk for Adverse Pregnancy Outcomes

*Use of this antifungal agent was associated with excess risk for spontaneous abortion and, at higher doses, for fetal cardiac defects.*

Fluconazole is most commonly prescribed for vaginal yeast infections, which can be resolved with a single 150-mg dose. Higher doses are indicated for systemic fungal infections. To evaluate the safety of fluconazole during pregnancy, Canadian investigators conducted a nested case-control study in a cohort of 440,000 pregnant women who delivered in Quebec from 1998 through 2015. Fluconazole dosages were stratified into low (≤150 mg) or high (>150 mg).

Overall, <1% of women received fluconazole during pregnancy; of these, 70% received a single low dose. Compared with no fluconazole exposure, low-dose and high-dose exposure were associated with excess risk for spontaneous abortion (adjusted odds ratios, 2.2 and 3.2, respectively). High-dose fluconazole was also associated with significantly higher risk for fetal cardiac septal closure anomalies (OR, 1.8). Risk for several other congenital malformations was also increased with high-dose fluconazole, but because these events were rare, the associations were not statistically significant. Risk for stillbirth was unaffected by fluconazole, regardless of dosage.

**CITATION(S):** Bérard A et al. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. CMAJ 2019 Feb 19; 191:E179. (https://doi.org/10.1503/cmaj.180963)

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Obstet Gynecol 2019 Feb 4; 133:423

# For Medical Management of Uterine Fibroids, Consider Both Sides of the GnRH Coin

*In a Japanese trial, the GnRH antagonist relugolix was noninferior to the agonist leuprolide and induced amenorrhea faster.*

Medical management of uterine fibroids involves suppressing ovarian estradiol and progesterone production, thereby reducing fibroid size and resolving heavy uterine bleeding. Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide (also known as leuprorelin) initially *stimulate* ovarian activity but, with continued treatment, *suppress* this activity; therefore, up to 6 weeks are required to achieve a reduction in ovarian steroidogenesis. In contrast, GnRH antagonists rapidly suppress ovarian activity; moreover, they can be taken orally whereas GnRH agonists must be administered by injection. To evaluate the efficacy of an oral GnRH antagonist (relugolix) versus a parenteral GnRH agonist (leuprolide), researchers in Japan conducted an industry-sponsored noninferiority trial in which 281 women with uterine fibroids and heavy menstrual bleeding were randomized to relugolix (40 mg daily) or leuprolide (1.88 mg or 3.75 mg intramuscular injection every 4 weeks) for 24 weeks. The primary endpoint was reduction in pictorially self-reported blood loss.

Amenorrhea was induced more rapidly by relugolix than leuprolide (53% vs. 22% at 2–6 weeks of therapy). At 24 weeks, similar proportions of patients had substantial reductions in blood loss with relugolix (82%) and leuprolide (83%); thus, relugolix was noninferior to leuprolide. In addition, reductions from baseline in uterine volume (−51%) and increases in hemoglobin concentration (+1.5 g/dL) were equivalent in both groups.

**CITATION(S):** Osuga Y et al. Oral gonadotropin-releasing hormone antagonist relugolix compared with leuprorelin injections for uterine leiomyomas: A randomized controlled trial. Obstet Gynecol 2019 Feb 4; 133:423. (https://doi.org/10.1097/AOG.0000000000003141)

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## Which Anti-CGRP Antibody to Choose First for Chronic Migraine

*Galcanezumab shows promise in a phase III, double-blind, placebo-controlled study.*

Chronic migraine — defined as 15 or more days of headache a month — can be challenging to treat even at tertiary headache centers. Researchers conducted a randomized, placebo-controlled, manufacturer-funded, phase III trial of galcanezumab in chronic migraine. After a run-in and baseline period, the 1113 participants were randomized to receive two 120-mg injections monthly of galcanezumab, one each of galcanezumab and placebo, or placebo only, for 3 months. Patients receiving onabotulinum toxin A for chronic migraine were excluded.

Both galcanezumab groups had a significantly greater reduction in mean monthly headache days than placebo at follow-up (120 mg galcanezumab, −4.8 days; 240 mg, −4.6; placebo, −2.7 days) and a significantly greater mean percentage of patients with ≥50% improvement from baseline (28 vs. 15%). Injection site pain (reported by 7%) was the most common side effect.

**COMMENT:** Among the three antibodies FDA-approved for treating migraine, only galcanezumab and fremanezumab have published phase III clinical trial data in chronic migraine (N Engl J Med 2017; 377:2113). Although erenumab showed an impressive result of mean reduction of −6.6 days per month, it was tested only in phase II clinical trial for chronic migraine (Lancet Neurol 2017; 16:425). Comparing phase III trial data, galcanezumab did slightly better than fremanezumab at reducing headache days (−4.8 days vs. −4.6 days), but this difference is negligible. Galcanezumab was tested in patients with more-frequent headaches than fremanezumab was (mean headaches days per month, 19 vs. 16). The main limitation of the current study is a shorter time period of 3 months. So far the best overall reduction in monthly number of headache days (−8 days) was seen in the chronic migraine phase III trial of eptinezumab, which is the only intravenous treatment (https://investor.alderbio.com/news-releases/news-release-details/alder-announces-eptinezumab-significantly-reduces-migraine-risk).

The choice among the 3 antibodies depends on the patient's insurance provider. Erenumab binds the calcitonin gene-related peptide receptor, whereas the other two bind directly to the antibody. If one type fails to help, the other could be tried.

Dr. Tariq is Assistant Professor of Neurology, Johns Hopkins School of Medicine, and Director, Johns Hopkins Headache Center, Baltimore.

**CITATION(S):** Detke HC et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018 Dec 11; 91:e2211. (https://doi.org/10.1212/WNL.0000000000006640)

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## Guidelines Issued on Dementia and Driving

*Joe Elia, Physician's First Watch and Jennifer Rose V. Molano, MD*

*U.K. guidelines can also help clinicians in the U.S. and elsewhere in assessing and advising patients.*

Guidelines on talking about driving with patients suffering from dementia or mild cognitive impairment have been issued by a working group from several U.K. organizations, including the Royal College of Psychiatrists and Royal College of General Practitioners.

Although specific in its legal particulars to the U.K., the document offers questions that all clinicians can use in talking with patients and family members to assess the driver's safety (see page 26 of the guidelines).

The National Institutes of Health provides U.S.-specific resources for both patients and clinicians: https://www.nia.nih.gov/health/driving-safety-and-alzheimers-disease.

**COMMENT — NEUROLOGY:** *Jennifer Rose V. Molano, MD*

The U.K. guidelines offer practical questions to assess safety and also address the psychosocial aspects of the decision-making process, including ways to offer support and potential alternatives for those who are not driving. In addition to reviewing their state laws, clinicians also can consider recommendations such as in-person license renewals, vision testing, or road testing in specific age groups (NEJM JW Neurol May 2018 and *Neurology* 2018; 90:e808).

**CITATION(S):** UK Guideline Development Group. Driving with Dementia or Mild Cognitive Impairment: Consensus Guidelines for Clinicians. 2018. (https://research.ncl.ac.uk/driving-and-dementia/consensusguidelinesforclinicians/Final%20Guideline.pdf)

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Mult Scler 2018 Dec 19

# Imaging Correlates of the Smoldering Multiple Sclerosis Plaque

*Slowly expanding lesions were more frequent in primary progressive MS.*

Chronic multiple sclerosis (MS) lesions are characterized by an inactive center and either a rim of activated microglia and macrophages filled with myelin (active) or a paucity of infiltrating lymphocytes, macrophages, and microglia (inactive). Active, smoldering plaques are thought to contribute to ongoing demyelination, axon loss, and disease progression. Investigators analyzed slowly expanding lesions (SELs) using imaging data from the phase III research supporting approval of ocrelizumab for treatment of relapsing-remitting (RR) and primary-progressive (PP) MS. More than 2300 patients were studied, including 1334 with relapsing and 555 with progressive disease. SELs were identified based on T1- and T2-weighted MRI sequences, where there was gradual radial expansion of at least 10 voxels.

Patients with PPMS had more SELs than those with RRMS (6.3 vs. 4.6) and a higher mean T2 volume of SELs (1838 mm$^3$ vs. 1223 mm$^3$). SELs were more often T1 hypointense compared with non-SELs, and the degree of T1 hypointensity was more prominent in the patients with PPMS.

**COMMENT:** A clearer picture of progression in MS is beginning to emerge from recent studies. Smoldering/expanding lesions are one piece of that puzzle. Factors contributing to MS progression are present from the start of the disease. In this study, early relapsing patients also had expanding lesions, albeit fewer than those with PPMS. We also know that other contributors to disease progression, such as meningeal inflammatory aggregates, subpial demyelination, neuronal drop out, microglia activation, and brain atrophy, are present at the beginning. With better imaging and biomarker correlates, the goal would be to identify patients whose early pathology is associated with disease progression and treat them more aggressively.

**CITATION(S):** Eliott C et al. Slowly expanding/evolving lesions as a magnetic resonance imaging marker of chronic active multiple sclerosis lesions. Mult Scler 2018 Dec 19; [e-pub]. (http://dx.doi.org/10.1177/1352458518814117)

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# Why Children and Teens in the United States Die

*Deaths in youth older than 1 year are often caused by unintentional injuries and occur most frequently in teens.*

Although death in childhood is uncommon, 20,360 children died in the United States in 2016. In the past century, the causes of death after the first year of life have changed dramatically. A review of 2016 U.S. surveillance data of the leading causes of deaths among children (aged 1–9 years) and adolescents (aged 10–19 years) showed the following:

- Motor vehicle crashes were the leading cause of death overall (20%) and in adolescents.
- Firearms accounted for 15% of deaths; 59% of these deaths were homicides, 35% suicides, and 4% unintentional.
- Cancer was the third leading cause of death (9%).
- Suffocation accounted for 7% of deaths.
- Drug overdose was the sixth leading cause of death.
- Death between ages 5 and 9 was rare; cancer was the predominant cause.
- The majority of deaths (68%) occurred in adolescents.
- Causes of death varied by age and geography; for example, drowning was the leading cause of death in ages 1 to 4, and firearm-related deaths were more common in rural areas.
- Disparities by race/ethnicity were found: Mortality rates from firearms and medical issues (e.g., heart disease) were highest in black youth, motor vehicle death rates were highest in Native American youth, and drug overdose death rates were highest in white youth.

**COMMENT:** These data are an important guide for pediatricians in educating families and patients about preventable causes of death in children and teens. Fencing swimming pools, locking firearms, avoiding distracted and impaired driving, and preventing and treating drug overdose would save many young lives.

**CITATION(S):** Cunningham RM et al. The major causes of death in children and adolescents in the United States. N Engl J Med 2018 Dec 20; 379:2468. (https://doi.org/10.1056/NEJMsr1804754)

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# Does Prophylactic Salpingo-Oophorectomy Also Reduce Risk for Breast Cancer?

*Further time-dependent analysis continues to indicate that the answer is no.*

Although earlier reports suggested that risk-reducing salpingo-oophorectomy (RRSO) in *BRCA1* and *BRCA2* mutation carriers also lowered risk for breast cancer, a more recent Dutch study using time-dependent analysis (which defined women as unexposed prior to RRSO and exposed following RRSO) found that RRSO did not reduce risk for breast cancer (*J Natl Cancer Inst* 2015; 107:djv033). Now, in a prospective cohort study, investigators followed 17,917 women (age at baseline, 18–79; 7.2% with *BRCA1* or *BRCA2* mutations) without known breast cancer at baseline for a median of 10.7 years, during which 1046 received diagnoses of incident breast cancer.

Taking the time exposed to RRSO into consideration, no association between RRSO and risk for breast cancer overall was identified (hazard ratio, 1.04; 95% confidence interval, 0.87–1.24). Stratifying by breast cancer risk based on family history, analyzing *BRCA1* and *BRCA2* mutation carriers separately, or accounting for use of post-RRSO menopausal hormone therapy did not reveal any subgroups of women in whom RRSO reduced breast cancer risk.

COMMENT: In *BRCA1* carriers who have completed childbearing, RRSO is recommended by age 35 to 40; for *BRCA2* carriers, delaying RRSO until age 40 to 45 may be suitable. Referring all such patients to a gynecologic oncologist to discuss surgery is appropriate. However, the current study did not report the proportion of participants undergoing risk-reducing bilateral mastectomy (RRM). Also, in the 2015 Dutch study cited above, women undergoing RRSO were less than half as likely to undergo RRM as those who did not have RRSO. Taken together, these findings imply that the ability to assess the independent impact of RRSO on breast cancer risk remains limited, leaving many clinicians in limbo regarding how best to counsel high-risk women when weighing the risks and benefits of RRSO.

CITATION(S): Terry MB et al. Risk-reducing oophorectomy and breast cancer risk across the spectrum of familial risk. J Natl Cancer Inst 2018 Nov 28; [e-pub]. (https://doi.org/10.1093/jnci/djy182)