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Women With *BRCA1* Mutations at Higher Risk for Endometrial Cancers

Neil Osterweil

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Women with *BRCA1* mutations who undergo risk-reducing ovary and fallopian tube removal without concomitant hysterectomy are at increased risk for serous or serous-like endometrial carcinoma, results of a long-term prospective study suggest.

Among 1,083 women with deleterious mutations in either *BRCA1* or *BRCA2* or both who underwent risk-reducing salpingo-oophorectomy (RRSO) without hysterectomy, there was no overall increase in uterine corpus cancers compared with the general population. Women with *BRCA1* mutations, however, showed increased risk for serous/serous-like endometrial carcinomas; these comprise only 10% of endometrial cancers but account for about 40% of endometrial cancer deaths, reported Catherine A. Shu, MD, of Columbia University, New York, and her colleagues (*JAMA Oncol*. 2016 Jun 30. doi: 10.1001/jamaoncol.2016.1820).

"Our results suggest that *BRCA1*+ women are at increased risk for serous/serous-like endometrial carcinoma," they wrote. "Although instability in the estimated magnitude of this risk remains, we believe that the possibility of this cancer should be considered when discussing the advantages and risks of hysterectomy at the time of RRSO in *BRCA1*+ women."

Salpingo-oophorectomy to reduce risk for breast, ovarian, and fallopian-tube cancers is a standard option for women with *BRCA* mutations, but it's unclear whether concomitant hysterectomy offers additional benefit.

To help clarify the issue, investigators at nine comprehensive cancer centers enrolled 627 women with *BRCA1* mutations, 453 with *BRCA2* mutations, and three with mutations in both genes who underwent RRSO without either prior or concomitant hysterectomy. They followed the patients for a median of 5.1 years from the date of ascertainment, receipt of *BRCA* testing results, or RRSO.

There were a total of eight incident uterine cancers over the course of follow-up. Compared with the expected 4.3 based on Surveillance, Epidemiology, and End Results (SEER) data, the observed-to-expected incidence ratio (1.9) was not statistically significant.

When the researchers stratified by subtype, no increased risk was found for endometrioid endometrial carcinoma or sarcoma.

However, there were five cases of serous/serous-like endometrial carcinomas occurring from 7.2 to 12.9 years after surgery. The affected patients included four women positive for *BRCA1* mutations and one positive for *BRCA2*.

In the SEER population, the observed-to-expected ratio for women with *BRCA1* was 22.2. For *BRCA2,* the ratio (6.4) was not statistically significant.

Tumor analysis of the three serous/serous-like tumors from women positive for *BRCA1* showed loss of the wild-type *BRCA1* gene and/or loss of protein expression.

Finally, to determine if the results could have been confounded by a history of breast cancer or exposure to tamoxifen (which is associated with a small but significant increase in risk for endometrial cancer), the researchers reviewed the serous/serous-

VIEW ON THE NEWS

Considering hysterectomy in women with *BRCA1* mutations

Is concomitant hysterectomy during RRSO [risk-reducing salpingo-oophorectomy] to reduce the risk for uterine cancer justifiable? It's difficult to fully define the additional risk and morbidity associated with combining a hysterectomy with RRSO; however, most surgeons would agree that this additional procedure does add some additional risk to women.

Along these same lines, overall mortality associated with hysterectomy is rare but possible. Recent studies suggest less intraoperative blood loss, lower wound complications, shorter hospitalization, and faster return to normal activity when this procedure is accomplished with a minimally invasive surgical approach, compared with an open laparotomy approach. This morbidity risk, and the rare but potential mortality risk, must be weighed against the risk for recurrence and death for women with a *BRCA* mutation who are diagnosed with uterine cancer.

This is particularly notable for those women diagnosed with serous carcinoma, who are recognized to harbor worse outcomes, even when they present at stage I. In this particular study, two of the five women with serous adenocarcinoma experienced recurrence, and one of these two died despite having stage IA disease. Serous carcinomas are biologically and clinically different from most endometrioid adenocarcinomas of the uterus, and the risk is essentially eradicated with hysterectomy.

Charles A. Leath, MD, MSPH, Warner K. Huh, MD, and **Ronald D. Alvarez, MD, MBA,** are in the Division of Gynecologic Oncology, University of Alabama at Birmingham. These comments were taken from an editorial they authored accompanying the report by Shu et al. (*JAMA Oncol*. 2016 Jun 30. doi: 10.1001/jamaoncol.2016.1773).

like subtype tumors. Four of these tumors occurred among 727 women with a history of breast cancer, compared with 0.26 expected (observed-to-expected ratio, 15.5). Among 356 women with no history of breast cancer, the expected incidence was 0.08, and the observed-to-expected ratio was not significant (12.6).

There were three serous/serous-like carcinomas among 273 women with tamoxifen exposure (expected rate, 0.12; observed-to-expected ratio, 24.4), and two occurred in 655 women without tamoxifen exposure (expected, 0.18; observed-to-expected ratio, 11.3).

The authors noted that with minimally invasive approaches, the additional surgical risks, mortality rates, and costs of adding concomitant hysterectomy to RRSO are relatively modest and may be an acceptable trade-off for some high-risk patients.

"If the present results are confirmed by future studies, hysterectomy with bilateral salpingo-oophorectomy may become the preferred risk-reducing surgical approach for *BRCA1*+ women," they wrote. "However, even if these results are confirmed, RRSO alone may still have a role for *BRCA1*+ women if strong reasons exist for uterine retention, such as dense pelvic adhesions or desire for future pregnancy using assisted reproductive approaches."

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Cochrane Review: Topical Steroid–Vitamin D Combo Best for Scalp Psoriasis

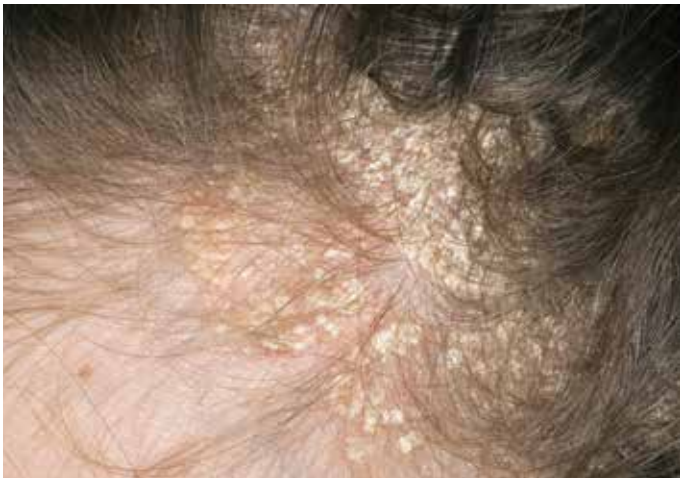
Bianca Nogrady

Combining a topical steroid and topical vitamin D to treat scalp psoriasis yields marginally better results than topical steroids alone, but both approaches have a similar safety profile, according to a Cochrane review.

The systematic review included 59 randomized, controlled trials of topical treatments for scalp psoriasis, representing a total of 11,561 participants of all ages, most of whom were followed for less than six months, according to Justin Schlager, MD, of the Charité–Universitätsmedizin Berlin, and coauthors (*Cochrane Database Syst Rev*. 2016. Issue 2. doi: 10.1002/14651858.CD009687.pub2).

Topical steroid monotherapy was found to be more effective than topical vitamin D for clearance, as assessed via the Investigator's Global Assessment scale of disease severity (risk ratio [RR], 1.82). Combining a topical steroid with vitamin D showed a small but statistically significant advantage over steroids alone, and an even greater advantage over vitamin D alone (RRs, 1.22 and 2.28, respectively).

Similarly, for treatment response, the use of a



Credit: Dr. P. Marazzi / ScienceSource

combination of a topical steroid and vitamin D showed the greatest benefit when compared with steroid monotherapy (RR, 1.15) and with vitamin D alone (RR, 2.31).

For monotherapy, corticosteroids were more than twice as effective as vitamin D alone for treatment response (RR, 2.09). The analysis also showed that corticosteroids of moderate, high, and very high potency were similarly effective.

Steroids were associated with a significantly lower risk for withdrawal due to adverse events than vitamin D (RR, 0.22). Reported adverse effects among steroid users included a burning sensation or irritation at the site of application, and among vitamin D users, pruritus, candidiasis, dermatitis, and erythema. In both cases, adverse effects were mostly limited to the application site.

The combination of vitamin D and topical steroids had a lower risk for withdrawal from adverse events than vitamin D alone, but showed a similar rate to steroid monotherapy.

"Given the similar safety profile and slim benefit of the two-compound combination over the steroid alone, monotherapy with generic topical corticosteroids may be fully acceptable for short-term therapy," the authors wrote. They noted that quality-of-life data was limited across all studies included in the analysis and called for more long-term assessments to address this gap.

"Regardless of the type of psoriasis, up to 79% of people with the condition present with scalp involvement, which has frequently been the first site to show symptoms of the disease," the authors pointed out.

Thirty of the 59 studies were either conducted or sponsored by the manufacturer of the study medication, and the authors described the overall quality of the studies as "moderate." Thirty-three studies were double blind, 14 were single blind, two had "third-party" blinding, six were open-label, and four did not report blinding information.

Disclosures: *The study was supported by the Universidade Federal de São Paulo, Brazil; the Universidade Federal do Rio Grande do Norte, Brazil; and the National Institute for Health Research, United Kingdom. Six authors and one clinical referee declared speakers' fees, research grants, and funding from the pharmaceutical industry. One author had no conflicts of interest to disclose.*

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Study Finds Emergence of Azithromycin-resistant Gonorrhea

Doug Brunk

Resistance to azithromycin, and to a lesser degree cephalosporin antibiotics, was observed in patients with gonorrhea, according to an analysis of data from a national surveillance system.

"It is unclear whether these increases mark the beginning of trends, but emergence of cephalosporin and azithromycin resistance would complicate gonorrhea treatment substantially," reported Robert D. Kirkcaldy, MD, of the CDC's Division of STD Prevention, Atlanta, and his colleagues. The results were published in *Morbidity and Mortality Weekly Report*.

Dr. Kirkcaldy and his colleagues evaluated 2014 data from the Gonococcal Isolate Surveillance Project (GISP), which the CDC established in 1986 to monitor trends in antimicrobial susceptibilities of *Neisseria gonorrhoeae* strains in the United States.

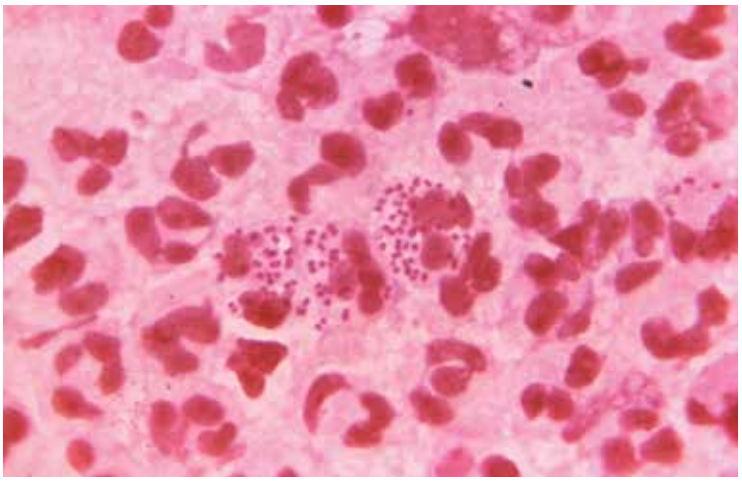
The *N gonorrhoeae* isolates are collected from the first 25 men with gonococcal urethritis who present at 27 participating STD clinics each month.

In 2014, a total of 5,093 isolates were collected. Among these, 25% demonstrated resistance to tetracycline, 19% to ciprofloxacin, and 16% to penicillin. At the same time, resistance to azithromycin increased from 0.6% in 2013 to 2.5%, predominantly in the Midwest.

Meanwhile, resistance to the cephalosporin antibiotic cefixime increased from 0.1% in 2006 to 1.4% in 2010 and 2011, fell to 0.4% in 2013, and increased to 0.8% in 2014. Resistance to the cephalosporin antibiotic ceftriaxone increased from 0.1% in 2008 to 0.4% in 2011, then decreased to 0.1% in 2013 and 2014.

"Local and state health departments can use GISP data to determine allocation of STD prevention services and resources, guide prevention planning, and communicate best treatment practices to health care providers," the researchers wrote. "Continued surveillance, appropriate treatment, development of new antibiotics, and prevention of transmission remain the best strategies to reduce gonorrhea incidence and morbidity."

Disclosures: The researchers reported having no financial disclosures.



Credit: CDC / Bill Schwartz

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Statins Improve Ovarian Cancer Survival

Bruce Jancin

Statin therapy was independently associated with a substantial survival benefit in women with ovarian cancer in an analysis of linked data from the Surveillance, Epidemiology, and End Results (SEER) registry and Medicare.

"This is the largest series ever reported supporting the anticancer effect of statin therapy on epithelial ovarian cancer with a concomitant improvement in overall survival," Dr. Tilley Jenkins Vogel said, presenting the study results at the annual meeting of the Society of Gynecologic Oncology. "A prospective study in ovarian cancer patients is warranted. Identification of biomarkers that may predict response to statins would help further select patient populations and guide therapy."

Dr. Vogel and her coinvestigators at Cedars-Sinai Medical Center in Los Angeles identified 1,510 women in the SEER registry who were diagnosed with epithelial ovarian cancer during 2007-2009, underwent primary surgical resection, and survived for at least 60 days post surgery. Forty-nine percent were stage III and 25% stage IV; 42% of the women were on a statin.

Mean overall survival in the statin users was 32.2 months, compared to 28.7 months in nonusers. In the stage III cohort, mean overall survival in statin users versus nonusers was 31.7 and 25.9 months.

In a multivariate analysis adjusted for potential confounders (age; race; heart disease and other comorbid conditions prior to cancer diagnosis; and use of platinum-based chemotherapy), statin therapy was independently associated with a 34% reduction in the risk for mortality. In women whose ovarian cancer histology was serous, statin use was associated with a 31% reduction in death; in those with nonserous histology, it was a 48% reduction, Dr. Vogel reported.

Diving deeper into the dataset, she found that the overall survival benefit was present only in the 89% of statin users who were on lipophilic statins (eg, atorvastatin or simvastatin). This is consistent with

other investigators' reports that the noncardiovascular benefits of statin therapy are largely restricted to this class of LDL-lowering agents.

An anti–ovarian cancer benefit for statin therapy appears to have biologic plausibility, according to Dr. Vogel. She and her coworkers have previously shown synergistic cytotoxicity in vitro when statins are administered concurrently with platinum chemotherapy.

"This effect is believed to be mediated by greater inhibition of cell proliferation, increased apoptosis, and modification of proteins in the RAS pathway," she said.

Rapidly growing cells, such as cancer cells, require cholesterol to synthesize cell membranes. It's hypothesized that one mechanism for statins' anticancer effect is that the drugs interfere with this process by reducing intracellular cholesterol levels, Dr. Vogel noted.

Disclosures: Dr. Vogel reported having no financial conflicts regarding this study, conducted without commercial support.

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Common Surgeries Linked to Chronic Opioid Use Among Opioid-naive Patients

M. Alexander Otto

Common surgeries increase the risk for chronic opioid use in opioid-naive adults, especially those using antidepressants or benzodiazepines before their operations and those with substance abuse histories, according to an insurance claims analysis from Stanford University (see Figure).

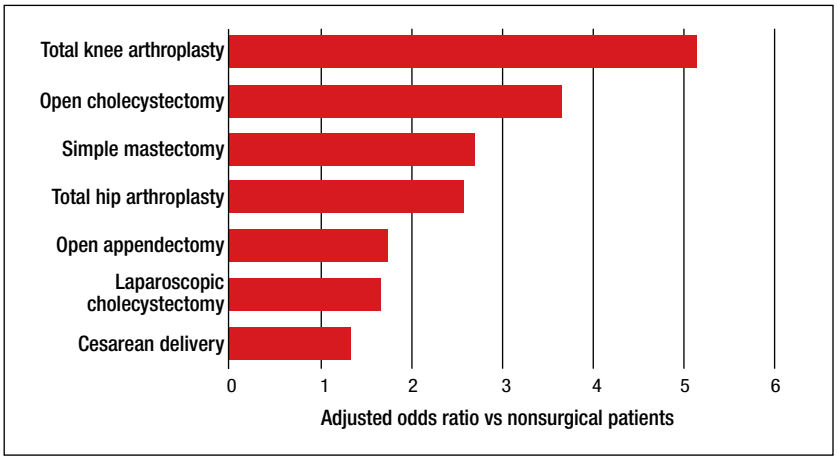
The researchers reviewed opioid prescribing in the first postop year—excluding the first 90 days—for 641,941 patients, and compared that information with opioid prescribing for more than 18 million adult patients who did not have surgery. None of the subjects had filled an opioid prescription in the previous year (*JAMA Intern Med.* 2016 Jul 11. doi: 10.1001/jamainternmed.2016.3298).

Chronic opioid use, defined as filling at least 120 days' worth of opioid prescriptions within the first year of surgery, ranged as high as 1.41% for total knee replacement, compared to 0.136% in the nonsurgical controls. After adjustment for potential confounders, knee replacement increased the risk fivefold; open cholecystectomy, almost fourfold; total hip replacement and simple mastectomy, almost threefold; and laparoscopic cholecystectomy and open appendectomy, almost twofold. Cesarean delivery increased the risk for chronic use by 28%.

With the exception of knee and hip replacements, "these procedures are not indicated to relieve pain and are not thought to place patients at risk for long-term pain," wrote Eric C. Sun, MD, PhD, of the Department of Anesthesiology, Perioperative and Pain Medicine at Stanford, and his colleagues. "Our results suggest that primary care clinicians and surgeons should monitor opioid use closely in the postsurgical period."

FIGURE

Risk of chronic opioid use after selected surgeries



Note: Based on data for 641,941 opioid-naive surgical patients and 18,011,137 opioid-naive nonsurgical patients.
Source: *JAMA Intern Med.* 2016 Jul 11. doi: 10.1001/jamainternmed.2016.3298

Preoperative antidepressants and benzodiazepines carried about the same risk for chronic use as alcohol abuse (odds ratio [OR], 1.83), while drug abuse history increased the risk even more (OR, 3.15). Male sex, age older than 50, and history of depression were also associated with chronic use on multivariate analysis. Meanwhile, transurethral prostatectomy, laparoscopic appendectomy, functional endoscopic sinus surgery, and cataract surgery did not increase chronic use risk.

"Surgical patients, particularly those at higher risk for chronic opioid use, may benefit from techniques to reduce the risk, such as multimodal analgesia and regional anesthesia, particularly in light of literature suggesting that these interventions may improve other perioperative outcomes," the investigators said. "Patients may also benefit from other preoperative and postoperative interventions, such as evidence-based psychobehavioral pain management skills."

It wasn't clear until now that even opioid-naive patients are at risk for opioid problems after surgery. Stanford's investigation is not the first to link surgery and opioid abuse, but previous studies tended to focus on patients with preexisting use and more painful operations.

The study included prescriptions for oral and patch fentanyl, hydrocodone, oral hydromorphone, methadone, morphine, oxymorphone, and oxycodone. Hydrocodone cough remedies and acetaminophen/codeine analgesics were excluded.

Nonsurgical patients tended to be younger than their surgical peers (mean, 42 vs. 44) and were more likely to be male (49% vs. 26%).

Disclosures: The authors had no disclosures. The work was funded in part by the Foundation for Anesthesia Education and Research and the Anesthesia Quality Institute. Claims data came from MarketScan (Truven Health Analytics).

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