Salpingectomy in Ovarian Ca Prevention on Trial

BY SUSAN LONDON

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

VANCOUVER, B.C. – A clinical trial is needed to assess the risk-benefit profile of salpingectomy for ovarian cancer prevention, said Dr. Barry Rosen.

A recent, serendipitous discovery, resulting from pathology examination of tissues removed during prophylactic salpingo-oophorectomy in patients with BRCA mutations, was that serous "ovarian" cancers actually arise from the fimbriae of the fallopian tubes.

"We didn't know it when we started doing [the surgery]," Dr. Rosen explained. "We sort of all of a sudden started to identify cancers, and most of them were in the tube. … All of a sudden, there has been a shift in the understanding that serous carcinomas do come from the tube."

In the wake of this new information, the Society of Gynecologic Oncology of Canada (GOC) issued two key recommendations, according to Dr. Rosen, professor of ob.gyn. and head of gynecologic oncology at the University of Toronto.

First, the GOC recommends that physicians discuss the risk-benefit profile of salpingectomy with women who are already having a hysterectomy or seeking irreversible contraception. "We don't come out and say 'Do it,' " he noted. "But we are coming out to say that it makes sense, and you should discuss it, and in that discussion, if it makes sense, that you should go ahead and proceed to do it."

Second, the GOC recommends that, given the lack of evidence, a national study of ovarian cancer prevention through salpingectomy be a priority of the society. "We want to collect the evidence to support this, and we want to be sure that the evidence supports it before we really jump in and say everybody should be doing this," Dr. Rosen said.

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DR. ROSEN

"I don't think there's any question that salpingectomy makes sense. Serous carcinoma is the worst [ovarian] cancer, it's the most common cancer, [and] it causes more deaths than any," he commented. "So if you can prevent this cancer, you are probably going to have the biggest impact on ovarian cancer that we have today. Bigger than screening, for sure – we know [screening] doesn't work. But bigger than any treatment and any of the fancy treatments that are coming out that are really very expensive treatments."

Adding salpingectomy to other, planned surgeries could potentially provide preventive benefit to tens of thousands of women annually in Canada alone. For starters, roughly 47,000 Canadian women undergo hysterectomy nationally each year. Removal of the ovaries and tubes at the same time is fairly standard for those who are postmenopausal. "But it's the premenopausal women for whom you would have the benefit of taking out the tubes and leaving the ovaries so that they could continue to have their hormone function," he noted.

And the procedure could be offered even more widely. For example, approximately 10,100 new cases of colon cancer are diagnosed annually among Canadian women, many of whom undergo pelvic surgery as a result.

There are many "other situations where urologists or general surgeons are doing surgery, so I don't think we have to limit this discussion to gynecologists," commented Dr. Rosen. "We need to expand it to all disciplines that may operate in the pelvis, because a surgeon can take out the tubes as well as we can."

When asked by an attendee whether it might perhaps be better to recommend simpler distal salpingectomy instead of total salpingectomy, he expressed reservations.

"While the belief is that most of these cancers arise in the fimbriated end, there are some that do arise further up the tube." Additionally, "we have to be careful if we put in the word 'distal.' We also have to define what distal is. So it's trickier than you think."

Dr. Rosen offered a few notes of caution from his own perspective. "Salpingectomy at open hysterectomy is different than at laparoscopic hysterectomy or tubal ligation," he said. "It's pretty simple if you have an open case to be able to put your favorite clamp across the tube and remove it; laparascopically, [for some it may be] a little bit more difficult. … When doing the procedure, you need to treat this as a surgical procedure, and not just think, 'Oh yeah, we'll just take out the tubes,' and find yourself in some trouble with bleeding or an injury of some sort."

Also, the medical profession must decide what level of complications is acceptable. "I don't know the answer to that, but we need to know what the complication rate is, and we do know that there will be complications," Dr. Rosen said.

Finally, the new recommendations are currently based on a hypothesis, not on evidence. "There are other situations in our history in medicine where physicians really believed something very strongly and proceeded with limited information," he noted, citing by way of example the use of diethylstilbestrol in the 1940s and 1950s to prevent miscarriage, and its subsequent linkage to cancer. "We need to be sure that we get the evidence. I believe that we need to evaluate this in some form of clinical trial."

Should salpingectomy prove to be effective and adequately safe for preventing ovarian cancer, it would constitute a major turning point in a disease that still has a poor prognosis, he said.

To be sure, treatments have improved steadily over the past 25 years, prolonging life and improving its quality. "We can continue to expect improvements, but I think they are going to be gradual and they are going to be small," he said.

Efforts to detect the cancer early through screening have thus far not panned out. Three large screening studies were initiated in 1985-2001, one each in the United Kingdom, Japan, and the United States.

Results from the last – the PLCO (Prostate, Lung, Colorectal, and Ovarian) trial, which tested screening with cancer antigen 125 (CA 125) and transvaginal ultrasound – were recently reported (JAMA 2011;305:2295-303). They showed that 20 surgeries had to be performed to detect one cancer, and the rate of major complications was 20% among patients who underwent surgery. And at the end of the day, there was no reduction in ovarian cancer mortality.

Results of the U.K. study, which is using a different, serial multimodality approach to screening, are expected in the 2014 timeframe.

Prevention efforts up to this point have been limited to birth control pills and to BRCA testing with prophylactic surgery for carriers, but this group makes up only about a tenth of all patients with ovarian cancer, he noted.

Dr. Rosen said he had no relevant financial disclosures. ■

BRCA2 Gene Mutation Tied to Better Survival in Ovarian Ca

BY SHARON WORCESTER

FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH

ORLANDO – Ovarian cancer patients with BRCA1 or BRCA2 gene mutations have better survival than do those with neither mutation, and those with the BRCA2 mutation have better survival than do those with the BRCA1 mutation, according to the findings of a large, multicenter study.

The findings confirm the results of several prior smaller studies showing a survival advantage in mutation carriers vs. nonmutation carriers, and they provide the first direct evidence that BRCA1 and BRCA2 mutations have differing effects on survival, Kelly L. Bolton reported.

She and her colleagues studied 3,531 women with invasive epithelial ovarian cancer who were enrolled in one of 24 studies in the United States, Europe, Israel, and Asia, and for whom survival data were available. Included were 1,178 women with BRCA1, 367 with BRCA2, and 1,986 who were BRCA-negative.

The 5-year survival was 36% in those with no mutation, 46% of those with the BRCA1 mutation, and 61% of those with the BRCA2 mutation, after adjustment for stage, grade, histology, and age at diagnosis, said Ms. Bolton, a predoctoral fellow at the National Cancer Institute.

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Major Finding: The 5-year survival was 36% in those with no BRCA mutation, 46% in those with the BRCA1 mutation, and 61% in those with the BRCA2 mutation, after adjustment for stage, grade, histology, and age at diagnosis.

Data Source: A large, multicenter study investigating the impact of germline BRCA1 and BRCA2 mutations in 3,531 women with invasive epithelial ovarian cancer.

Disclosures: Ms. Bolton said she had no relevant financial disclosures.

The difference in survival between the BRCA1 mutation carriers and those with no mutation was modest (hazard ratio, 0.84), although not statistically significant. However, the difference between the BRCA2 mutation carriers and both the noncarriers and the BRCA1 mutation carriers (after adjustment for age at diagnosis) did reach statistical significance (HR, 0.57 and 0.69, respectively). Even after the exclusion of all but high-grade, advanced-stage serous cases, the survival differences persisted, Ms. Bolton reported.

A possible explanation for the differences, based on in vitro work and some retrospective trials, may lie in patients' responses to chemotherapy; those with the BRCA2 mutation may have an improved response, but unidentified biological differences among BRCA1 carriers, BRCA2 carriers, and noncarriers could also be driving the association, she said.

The BRCA1 and BRCA2 mutation carriers in this study did not differ in regard to tumor stage, grade, or histology. Compared with noncarriers, however, BRCA1 carriers were younger and BRCA2 carriers were older at diagnosis.

Furthermore, compared with noncarriers, BRCA1 and BRCA2 carriers were more likely to present with advanced-stage disease, high-grade disease, and serous disease.

"The findings don't have any immediate impact on clinical practice, but they do have important implications [for both] clinical prediction and also trial design, particularly for clinical trials," Ms. Bolton said, noting that although germline mutations in the BRCA1 and BRCA2 genes are rare in the general population, they are present in 10%-15% of those with ovarian cancer. ■