Origin of Ovarian Cancer May Have Implications for Screening

By Rabiya S. Tuma

Ovarian cancer, like most malignancies, is named for the organ from which it arises. At least that was what clinicians and scientists thought. More recently, however, scientists have discovered that some ovarian cancers develop in the fallopian tube and then spread to the ovary. The proportion and characteristics of ovarian cancers that start in the tubes remain a matter of debate, but most experts agree that a tubal origin may make screening for ovarian cancer more difficult than previously thought.

Researchers initially hypothesized that serous ovarian cancer, which is the most common subtype of the disease, arose within cysts on the surface of the ovary. Yet when investigators looked for precancerous lesions in the ovaries removed during prophylactic surgery from women at high risk for the malignancy, they found very few lesions, fewer than expected in a population with such a high incidence of ovarian cancer.

With the relative absence of precursor lesions in the ovary itself, some researchers started looking for other sources for the cancers, including the fallopian tubes. In one study, Christopher P. Crum, M.D., professor of pathology at Harvard Medical School and director of women’s and perinatal pathology at Brigham and Women’s Hospital in Boston, examined the fallopian tubes of 13 women with BRCA mutations who underwent prophylactic surgery. He identified five early adenocarcinomas, three of which were noninvasive, and four of which involved the feathery tips of the tube, called fimbria, that brush against the ovary.

On the basis of those data and other studies that showed similar trends—and the fact that fallopian tube cancer is rare, even in the high-risk BRCA population—Crum and others concluded that at least a significant proportion of ovarian cancers start in the fimbria.

“If you take ovarian cancers in general, about 70% are high-grade serous ovarian cancers, which is the cancer that causes most deaths,” Crum said. “For about 45%–55% of those, I think you can make a reasonable case of [the cancer’s] arising in the fallopian tubes. At least we can find changes in the fallopian tubes to argue that it might have started there.”

Not everyone agrees that the percentage is that high. Robert Bast, M.D., vice president for translational research at the University of Texas M. D. Anderson Cancer Center in Houston, notes that whereas some ovarian cancers seem to coat the organ, most appear to involve the ovary itself. Those, he thinks, arise in the ovary. Therefore he estimates that closer to 10%–20% of ovarian cancers originate in the fallopian tubes.

On the other hand, some researchers think that the proportion may be even larger than Crum estimates. “I think it could be an explanation for the 25%–75% early–late diagnosis split,” said Michael J Birrer, M.D., Ph.D., professor of medicine at Harvard Medical School and director of gynecologic medical oncology at Massachusetts General Hospital Cancer Center in Boston. In other words, he hypothesizes that the 25% of ovarian cancers that are diagnosed as stage I or II tumors and that tend to respond well to surgery arise in the ovary, whereas the remaining 75%, which are diagnosed as advanced disease and are associated with a particularly poor prognosis, arise in the fimbria.

Birrer readily acknowledges that he doesn’t have many data to back up that hypothesis at this point, but he thinks it
is consistent with data that do exist and with what he sees in the clinic. For example, tubal ligation is associated with a 50% reduction in the risk of ovarian cancer. Also, he has had several high-risk patients who received CA125 serum marker tests and ultrasound every 6 months and yet suddenly showed up with stage III or IV disease. It is anecdotal evidence, he concedes. But it is also consistent with the idea that a small tumor could form in the fimbria, which is open to the ovarian surface and peritoneum, and then suddenly give rise to widespread disease.

**Molecular Differences?**

If the idea that aggressive cancers arise in the fallopian tube and less aggressive ones in the ovary itself is correct, one might hope to find molecular differences in the two tumor types, even when both are stage I or II. With that in mind, Birrer’s group, as well as several others, have been using genomic techniques to examine ovarian cancer tumors.

In one such study, Andrew Berchuck, M.D., director of gynecologic oncology at Duke University Medical Center in Durham, N.C., and colleagues used gene expression microarrays to study 54 ovarian tumors. In collaboration with Vermilion, a molecular diagnostics company, they found panels of markers that could detect both early- and advanced-stage tumors, even though those different stages are likely to have different gene expression patterns. Bast, who serves on the advisory board of Vermilion, said that such panels should help detect less bulky stage III disease, which is associated with better outcome than bulkier disease. The challenge remains, though, to identify markers that reveal subclinical cases, he said.

In addition to serum biomarkers, investigators have been testing the utility of ultrasound for ovarian cancer screening. If many ovarian cancers do come from the fallopian tube, as most experts agree, then that may also limit the value of ultrasound. Not only has ultrasound imaging focused on the ovary itself, which might be the wrong location, but the tubal precursor lesions are much smaller than the early tumors were expected to be in the ovaries, even when the tubal lesions appear able to spread to the peritoneum and ovary. “How do you detect something that is four to five cell layers thick on the tube?” Crum asked. “There is no imaging for that.”

Berchuck too emphasizes that the premise underlying ultrasound-based screening is the presence of an ovarian mass. If the tumor cells spread from the tube and into the peritoneum and ovary quickly, with no large precursor mass, that premise may be misleading. “The tumor cells may get out of the tube and explode with carcinomatosis. The whole idea that it has distinct molecular changes, then the biomarkers developed from those low-risk cases may not be useful in detecting early-stage aggressive cancers, according to Birrer.

Not everyone thinks that the situation is so dire. Bast and colleagues currently have a report in press describing a study in which they tested 96 possible biomarkers. In collaboration with Vermilion, a molecular diagnostics company, they found panels of markers that could detect both early- and advanced-stage tumors, even though those different stages are likely to have different gene expression patterns. Bast, who serves on the advisory board of Vermilion, said that such panels should help detect less bulky stage III disease, which is associated with better outcome than bulkier disease. The challenge remains, though, to identify markers that reveal subclinical cases, he said.

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starts in the ovary and there is a mass in the ovary before you start carcinomatosis may not be right,” he said.

Two ongoing trials may eventually throw light on the question of current screening methods’ influence on mortality. Ian Jacobs, M.D., of the University College London, and colleagues are comparing the utility of two screening approaches, CA125 biomarker screening alone and CA125 and ultrasound vs. no screening in 200,000 women. The results are expected in 2013. In the United States, the National Cancer Institute’s Prostate, Lung, Colorectal, and Ovarian trial is comparing CA125 screening and ultrasound to usual care. With about 39,000 women in the intervention group, screening ended in 2006 and follow-up will continue for 10 years. These trials may answer some of the questions about the benefit of ovarian cancer screening in the general population. But if the skeptics are right, the screening protocols could detect many cancers at an early stage and still not have a large effect on mortality.

For Crum, the most important aspect of identifying early cancers in the tube is the opportunity to understand the natural history of ovarian cancer. By studying precursor lesions and the sequence of events that give rise to cancer in the tube, he thinks one might be able ultimately to identify risk factors. And that would mean scientists could start thinking about prevention, not just early detection or treatment.