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Tying Fallopian Tubes to Ovarian Cancer Risk

By Susan Jenks

Increasing evidence suggests that the fallopian tubes—once seen as an extremely rare site for cancer—could be the source of the most aggressive ovarian cancer.

Last April, investigators at the Dana–Farber Cancer Institute in Boston immortalized fallopian tube cells in the lab, inducing the process by which ovarian cancer progresses from these reproductive tubes to high-grade serous tumors in the ovary: the deadliest, most common form of the disease.

"For all those disbelievers out there, this hopefully is the nail in the coffin," said Jessica McAlpine, M.D., an assistant professor in the University of British Columbia's department of gynecology and obstetrics, referring to the April article in the *Proceedings of the National Academy of Sciences*. "Obviously, there's a need for further study, but we need to do something about it now."

In Canada, researchers have begun urging gynecologists to routinely remove the fallopian tubes in place of a tubal ligation, or during a hysterectomy, even if a woman is not at high risk for ovarian cancer. By convention, current practice leaves these tubes in place.

"For a woman who wants to have her tubes tied, she's already decided against having more or any children, so instead of tying the tubes, why not take them out?" McAlpine asked. "And, in a hysterectomy, it's easier to remove the fallopian tubes and keep the ovaries for their hormonal function. We think that reduces the risk not only for ovarian cancer but for other [gynecologic] cancers as well." Preserving ovarian function, especially in younger women, would also stave off premature menopause with all its attendant health risks, she said, including heart disease, osteoporosis, dementia, and stroke.

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Not So Fast

In the U.S., however, physicians are moving more slowly toward changing clinical practice, in part because doing so here is harder than in a uniform medical system such as Canada's. But before moving the measure into the general population, U.S. doctors want more proof that this step is reasonable for high-risk women. A small group of gynecologic oncologists is now drafting the parameters of a large clinical trial.

Jessica McAlpine, M.D.

"There's a lot of evidence that at least 60%–70% of serous tumors come from the fallopian tubes—but not all do, or at least we've been unable to show they do, as yet," said Ronny Drapkin, M.D., Ph.D., an author of the *PNAS* study and an assistant professor of pathology at Harvard Medical School.

That limitation contributes to the division between "physicians who are gun-shy about possibly missing one of these lethal cancers and others who think it's time to deploy our observations into the clinic where conceivably they could have a big impact."

As for reducing the risk in the general population, Drapkin warned that it will take many years to determine in the Canadian cohort, Drapkin warned, despite McAlpine's estimates that the change in surgical practice in Canada could reduce ovarian cancer risk by as much as 40% over 20 years. McAlpine said she based those estimates on data showing a 20% risk reduction "from what we're already doing in high-risk women," including monitoring families who have the BRCA gene mutations, to known risk reductions from removing the fallopian tubes in women undergoing hysterectomy or those who've opted for tubal ligation.

Complexity of Ovarian Cancer

According to the American Cancer Society, ovarian cancers will strike an estimated 21,990 U.S. women in 2011, some 15,460 of whom will die of their disease. Molecularly complex, most of these cancers escape early detection, and most are serous high-grade tumors that metastasize rapidly.

"There are really two types of ovarian cancers: indolent, slow-growing cancers and the other group, which represents a majority of them," said Jonathan Lancaster, M.D., Ph.D., chair of the department of women's oncology and deputy physician chief of the Moffitt Medical Group at H. Lee Moffitt Cancer Center in Tampa, Fla. "These tumors are nasty, aggressive, highly virulent, and go from normal to advanced stage very quickly." They are considered heterogeneous at both the clinical and molecular level. "What we know is that there are mutations all over the place in many, many genes," Lancaster said. "It's a messy [genomic] picture."

Although evidence that ovarian cancers arise in the distal fringes of the fallopian tubes (the fimbriae) may still lack definitive clinical proof, he and others said, a high probability exists that this is the case.

Besides studies documenting decreased ovarian cancer risk after hysterectomy or a tubal ligation, "most importantly, there's increasing molecular data showing that the areas that have been maimed lie in these tubes," Lancaster said. "We see precancerous changes and then these cancers float out to the ovary," where they take root.

The earliest lesion identified, the p53 mutation, the so-called guardian of the cell, occurs in nearly all ovarian cancers. These mutations lead to copy number alterations: too few or too many copies of a particular gene, Dana–Farber's Drapkin said. "Although many of the genes affected are the same as in other cancers, it's a disease of copy instability" resulting in lost or gained genetic pieces on every chromosome.

Given such complexity, Drapkin's lab and others are developing new model systems to study the biology of the fallopian tubes. They've developed an ex vivo system to look at what's normal physiology in these tubes—for example, by taking fallopian tube cells from women who've had them removed for reasons unrelated to cancer.

"We know these early cancers occur only in the fimbriae of the fallopian tube, and we needed to know what happens to these cells," Drapkin said. One question researchers asked is whether the follicular fluid causes injury during ovulation when the "egg explodes to the surface of the ovary."

"Sure enough, there is something," he said. Although the effect is transient in most women, those with BRCA mutations have a higher risk that this repetitive biological process damages their DNA, he said.

Eventually, as they learn more about other molecular characteristics, researchers plan to use genetically engineered mice to re-create changes that lead to the common defects seen in human ovarian cancers. "If we can do this, we can think about early detection," Drapkin said.

Early Detection With Autofluorescence

For now, an approach for early detection of ovarian cancer may lie in autofluorescence, an optical imaging technique already used to find occult cancers elsewhere in the body. McAlpine said they've tested the approach in Canada on about 50 patients so far after removing the women's fallopian tubes.

"We did see dark areas that corresponded to either tumors or precursor lesions," she said. After identifying them, the researchers put the tissue into formalin to study the DNA more closely.

Eventually, optical imaging could lend itself to early screening for these cancers, agreed Robert Burger, M.D., director of the women's center at Fox Chase Cancer Center in Philadelphia. But he sounded a note of caution, because unlike other cancers, where early screening works, "you don't see the explosive growth you see in this disease."

Why that occurs is unknown. Some women with ovarian cancer do well despite this, Burger said, but "the answer is to be proactive, to implement prevention."

"I think if a woman has completed childbearing and is having a hysterectomy or any type of abdominal surgery, taking out the fallopian tubes should be considered strongly," Burger said. "We've known about deleterious mutations with BRCA1 and BRCA2 for some time, but they are present in at most only 10% of women destined to develop epithelial ovarian cancers."

From a surgical standpoint, considering tubal ligation makes no sense, Burger said, because removing the fimbriae—a simple laparoscopic procedure—makes the tube nonoperational.

Feasibility Study To Address Other Questions

In recent months, Burger has worked with a small group of gynecologic oncologists from Dana–Farber and Memorial Sloan–Kettering Cancer Center, among others. The team is drafting a feasibility study that would complement the work in Canada, in the hope of answering such questions as "How much would I have to reduce the risk to consider [fallopian tube removal] a clinically beneficial method?"

Several clinical trial ideas are under consideration, he said, but for now the group is looking at the feasibility of a large, prospective epidemiologic study in women who've completed childbearing or choose to have a tubal ligation.

For these women, fallopian tube removal seems the clear choice, Berger said. "The harder question is whether women not already having surgery should do this, or if you find out you can reduce risk, should you consider this as an intermediate step—removing the fallopian tubes first and then the ovaries later on?"

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