Researchers identify early ovarian cancers

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Ovarian cancer kills nearly 15,000 women in the United States each year, and fewer than half of the women diagnosed with the disease survive five years. A screening test that detects ovarian cancer early, when it is still treatable, would likely reduce the high mortality, yet scientists have not known where the tumors originate or what they look like. Now, researchers at Fox Chase Cancer Center think they have answered both questions. The study, published on April 26th in *PLoS ONE*, reports that they have uncovered early tumors and precancerous lesions in cysts that fold into the ovary from its surface, called inclusion cysts.

"This is the first study giving very strong evidence that a substantial number of ovarian cancers arise in inclusion cysts and that there is indeed a precursor lesion that you can see, put your hands on, and give a name to," says Jeff Boyd, Ph.D., Chief Scientific Officer at Fox Chase and lead author on the study, which also involved colleagues at the Memorial Sloan-Kettering Cancer Center. "Ovarian cancer most of the time seems to arise in simple inclusion cysts of the ovary, as opposed to the surface epithelium."

Clinicians and researchers have been looking for early ovarian tumors and the precancerous lesions from which they develop for years without success. In this study, Boyd and colleagues used a combination of traditional microscopy and molecular approaches to reveal the early cancers.

"Previous studies only looked at this at the morphologic level, looking at

a piece of tissue under a microscope," Boyd says. "We did that but we also dissected away cells from normal ovaries and early stage cancers, and did genetic analyses. We showed that you could follow progression from normal cells to the precursor lesion, which we call dysplasia, to the actual cancer, and see them adjacent to one another within an inclusion cyst."

To learn where and how the tumors arise, the team examined ovaries removed from women with BRCA mutations, who have a 40% lifetime risk of developing ovarian cancer, and from women without known genetic risk factors. In both groups, they found that gene expression patterns were dramatically different in cells in the inclusion cysts compared to the normal surface epithelium cells, including increased expression of genes that control cell division and chromosome movement.

Moreover, when they used a technique called FISH (fluorescence in situ hybridization), which can be used to identify individual chromosomes in cells, they saw that cells from very early tumors and precursor lesions frequently carried extra chromosomes. In fact, the team found that 9% of the normal cells isolated from the cysts had extra chromosomes, even though the tissue appeared completely benign under the microscope. By contrast, virtually none of the cells isolated from the surface of the ovary, which was previously thought to be the site of early ovarian cancers, carried extra chromosomes.

With these new data on the origin of ovarian cancer in hand, Boyd and others can now start to develop screening tests, perhaps based on molecular imaging, that could be used to detect early ovarian cancers in asymptomatic women.

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