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JIM FRAZIER

Biomarkers warn of a "silent killer"

High or low levels of certain proteins can signal the likelihood of ovarian cancer.

Epithelial ovarian cancer ranks as the most lethal of gynecological malignancies. It is only 10 percent as common as breast cancer, but its mortality rate is three times as high. The reason is simple: routine mammography and breast examinations can catch breast cancer early, but no such screening exists for ovarian cancer in its early stages. With few early symptoms, the disease passes under the medical radar until it has reached later stages of malignancy, and therapeutic options are often limited.

Now a group headed by Gil Mor, M.D., Ph.D., associate professor of obstetrics, gynecology and reproductive sciences, has found a way to detect the "silent killer" in its earliest stages, according to a report in May in the *Proceedings of the National Academy of Sciences*. The researchers at Yale, George Washington University and the Nevada Cancer Institute devised a still-unapproved screening test that measures levels of four cancer-related proteins—leptin, prolactin, osteopontin and insulin-like growth factor II (IGF-II)—in blood samples. These biomarkers are proteins that change in response to several different forms of cancer, perhaps as part of the immune response. "Our strategy is unique in that we are using a combination of proteins representative of how the total system reacts to cancer, rather than focusing on one protein," said Mor. Previous studies had identified each of the four proteins as possible biomarkers, but Mor's team found that individually none of the proteins served as a reliable indicator of cancer.

The researchers began with 169 proteins linked to epithelial ovarian cancer. They then narrowed the list to 35 proteins that were either far more or far less prevalent in women with advanced cancer than in healthy women. They further refined the biomarker pool to the four proteins, two of which are consistently overproduced (prolactin and osteopontin) and consistently underproduced (leptin and IGF-II) in women with cancer.

To put these findings to clinical use, women need only have blood drawn. Levels outside of the normal range of two or more of the biomarkers predict cancer. Follow-up analyses, such as ultrasound, can verify the diagnosis.

In a preliminary study of more than 200 women, the screen accurately detected ovarian cancer in 95 percent of cases. The specificity of the test—those correctly diagnosed as disease-free—also stood at 95 percent, but Mor stressed that the test is not ready for screening the general population. "Because this disease is relatively rare, a specificity of 95 percent means that 5,000 out of every 100,000 women tested by this method would give a false-positive result. That's not acceptable," he said. To increase the screen's specificity to an acceptable 99.6 percent, Mor's team is looking at adding three more proteins to the biomarker pool.

—Kara Nyberg



AUTUMN 2005
yale medicine

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