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Obese women with large bellies may be at risk of developing a different subtype of breast cancer than those with widespread fat accumulation, according to a new study published in *The Oncologist*. This suggests that the link between breast cancer and obesity may be more complex than previously thought.

The study on women from Northern and Eastern China found that women who accumulated fat around their internal organs (visceral), measured by belly fat, were predisposed to develop a different subtype of breast cancer than those that accumulated fat more widely around their thighs, hips and buttocks (subcutaneous). The team also found that being obese before the menopause raised breast cancer risk in these women, confirming a known difference between Asian, black and white women.

Breast cancer is the most common cancer among women in China and the fifth leading cause of cancer-related deaths. Obesity is a well-known risk factor, which can be partly mitigated by lifestyle changes and the use of drugs like Tamoxifen in high-risk women. However, long-term drug use has side effects, and Tamoxifen only works for women whose breast cancer cells possess receptors for the hormone estrogen on their surface (ER+).

“It was believed that obesity was more strongly related to ER+ than ER- breast cancer,” explains corresponding author Zhigang Yu at the Second Hospital of Shandong University in China. Based on previous studies, Yu and his colleagues suspected that women’s risk of developing ER+ or ER- breast cancer varied with how fat was distributed throughout their body.

To test this theory, they recruited 1316 Han Chinese women aged between 25 and 70 from 21 hospitals in Northern and Eastern China who were newly diagnosed with breast cancer. They took body measurements and collected data on their reproductive and medical history, including whether they had been diagnosed with ER+ or ER- breast cancer. The women were compared with a control group of healthy in-patients attending the hospitals for a physical examination.

Yu and his colleagues found that women with a high body-mass index (BMI), providing a measure of subcutaneous fat, were more likely to have ER+ breast cancers, especially if they

were premenopausal. In contrast, women with a high waist-hip ratio (WHR), providing a measure of visceral fat, were more likely to have ER- breast cancer, especially if they had passed the menopause. This greater risk of developing ER- breast cancer for women with a high WHR held even if they didn't have a high BMI.

"A possible reason is that subcutaneous fat is involved in estrogen production, which may promote ER+ breast cancer," says Yu. "Visceral fat is more closely related to insulin resistance and may be more likely to promote ER- breast cancer."

Higher BMIs were not found to protect the Chinese women from breast cancer before the menopause, in contrast to findings from studies on black and white women. "I think there are two reasons for this," says Yu. "First, compared to western women, premenopausal Asian women, including Chinese women, tend to be slender, and fat mass may have more effects. Second, Asian women are more likely to become obese by accumulating visceral fat; this is quite different from western countries, where women are more likely to accumulate subcutaneous fat."

Based on their findings, Yu and his colleagues advise clinicians to evaluate ER+ breast cancer risk in obese women before prescribing Tamoxifen. "Considering that Tamoxifen cannot prevent ER- breast cancer, women with high WHRs may not benefit," says Yu. "And, more interestingly, it is the different patterns of fat distribution, visceral fat and subcutaneous fat, that may contribute to the distinct effects of obesity type, and this speculation provides a novel perspective for further study as to the interaction between obesity and breast cancer."

He also recommends more research into the effect of other breast cancer risk factors, such as insulin resistance and inflammation, in obese women, as well as the development of tools for predicting which high-risk women may develop ER+ and ER- breast cancers.

"Breast cancer is today becoming pandemic and, contrary to conventional wisdom, the global obesity epidemic is not restricted to industrialized societies. In developing countries like China, the combination of breast cancer and obesity can provoke severe health and economic consequences," says Eduardo Cazap, director of the Latin America and Caribbean Society of Medical Oncology in Buenos Aires, Argentina, who is a section editor of *The Oncologist* and was not involved in the study. "The findings provided by Yu and his colleagues may contribute to improving breast cancer prevention in many countries."

“Obesity is the greatest public health challenge of the 21st century, with implications for cancer, cardiovascular disease, diabetes and a host of other health conditions,” says Gabriel Hortobágyi, professor in the Department of Breast Medical Oncology at MD Anderson Cancer Center in Houston, TX, who is another section editor of *The Oncologist* and was not involved in the study. “As we learn more about the complex etiology and pathophysiology of obesity, it is becoming clearer that it is not a single pathological entity, but a more complex syndrome with varying implications for health, risk and preventive interventions.”

Full citation: "Distinct effects of BMI and WHR on risk of breast cancer by joint estrogen and progestogen receptor status: Results from a case-control study in Northern and Eastern China and implications for chemoprevention” Fei Wang, Liyuan Liu, Shude Cui, Fuguo Tian, Zhimin Fan, Cuizhi Geng, Xuchen Cao, Zhenlin Yang, Xiang Wang, Hong Liang, Shu Wang, Hongchuan Jiang, Xuening Duan, Haibo Wang, Guolou Li, Qitang Wang, Jianguo Zhang, Feng Jin, Jinhai Tang, Liang Li, Shiguang Zhu, Wenshu Zuo, Zhongbing Ma, Fei Zhou, Lixiang Yu, Yujuan Xiang, Liang Li, Shuohao Shen, Zhigang Yu. *The Oncologist*. Published Online: September 14, 2017; DOI: 10.1634/theoncologist.2017-0148.

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