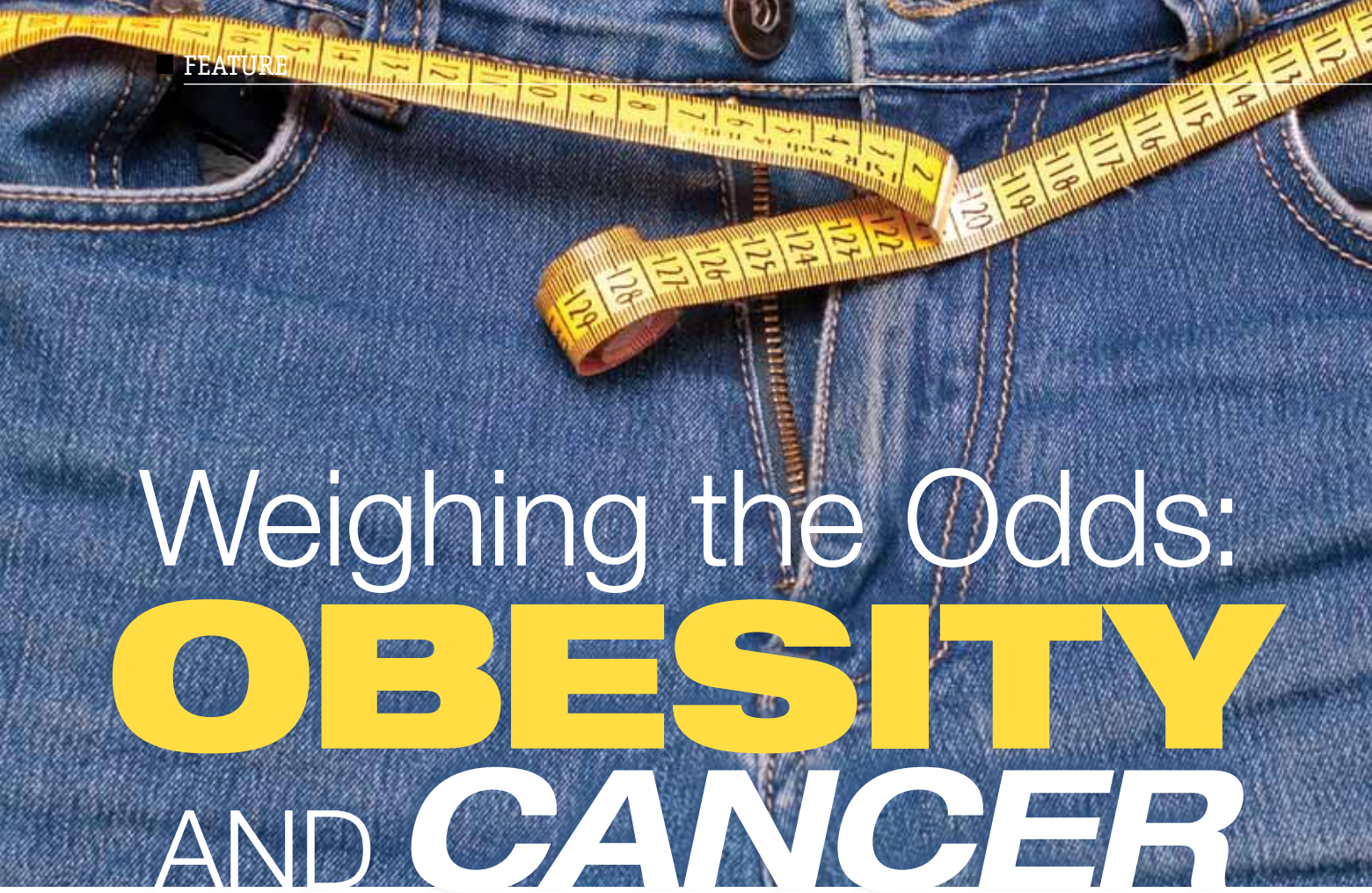

Weighing the Odds: OBESITY AND CANCER

By Margie Patlak*

A rising tide of cancer cases may be in store given the current obesity epidemic in the United States. Mounting evidence exists that fat tissue triggers the production of hormones and other compounds that fuel the growth of certain cancers. On a more positive note, the new findings suggest that diabetes treatments, such as metformin, may stem the growth of tumors, and that as many as one-fourth of cancers may be prevented by keeping a close watch on our waistlines.

"The epidemiologic evidence is pretty sound now on the relation between obesity, in particular abdominal obesity, and increased cancer risk," said Frank Visseren, M.D., Ph.D., of the University Medical Center Utrecht in the Netherlands.

Over the past 5 to 10 years, several large epidemiology studies have consistently linked being overweight or obese with a greater risk of developing certain malignancies such as postmenopausal breast, endometrial, esophageal, colon, kidney, liver, pancreatic, and gallbladder cancers. Other studies show that obesity is associated with developing more aggressive forms of prostate and breast cancer, and that extra pounds are tied to poorer outcomes for many tumors.

Intriguingly, how much being on the hefty side increases the risk of developing cancer varies by tumor type, gender, and menopausal status. Women who are obese have nearly triple the risk of developing endometrial cancer than those of normal weight; obesity increases the risk of their developing postmenopausal breast cancer by 40%. Obese men have about a 24% higher risk of colon cancer, but obesity raises that risk in women by only about 10% and does not appear to affect the risk for developing some tumors, such as premenopausal breast cancer.

Part of the variability in increased risk is explained by how fat tissue fosters tumors. Animal, laboratory, and clinical studies suggest the main culprits that tie fat tissue, especially abdominal fat, to various cancers are insulinemia, excess production of sex hormones, and inflammation. Although these are independent risk factors for cancer, they also interact in a complex web of cell signaling.

Tipping the Scales with Insulinemia

Excess abdominal fat induces high blood levels of insulin and type 2 diabetes mellitus (T2DM), which epidemiology studies show are risk factors for several malignancies, including breast, colon, pancreatic, prostate, and postmenopausal breast cancers. Laboratory studies comple-

ment those findings, showing that high serum insulin levels promote greater production and activity of insulin-like growth factor (IGF)-I. This stimulates cell proliferation and curbs cell death through biochemical pathways notorious for causing the growth and spread of various tumors. Indeed, cells of colon and prostate cancers, whose risk rises with obesity, have more IGF receptors, suggesting that IGF-I incites their growth.

Metabolic abnormalities that stimulate cancer are more likely to occur in abdominal obesity, which men are more prone to, than in the fat tissue that tends to accumulate in the thighs and buttocks of obese women. This difference in fat distribution might explain gender differences in how much obesity increases the risk of certain cancers, although this is currently speculation, according to Dr. Visseren.

Off-Kilter Sex Hormones

High insulin blood levels indirectly cause greater availability of the sex hormones estrogen, testosterone, and other androgens, which are known to trigger many tumors, including breast, prostate, and endometrial cancers. Fat tissue releases leptin, which cultivates estrogen synthesis and cell proliferation in breast cancer cell lines, and higher circulating leptin levels in women are significantly linked to an increase in breast cancer. Heightened leptin blood levels also boost colon cancer risk.

Fat tissue, including that found in the breast, can also produce estrogen by using its store of the enzyme aromatase to convert androgens into estrogens. Such local estrogen production can boost its levels in breast tumors so that they are as much as 10-fold higher than found in the circulation. Postmenopausal women who are obese tend to have breast cancer that is estrogen receptor–positive, supporting the link between boosted estrogen levels and tumor development. Obesity often causes a lack of ovulation in premenopausal women, which lowers their risk for breast cancer, and may explain why they are not susceptible to heightened breast cancer risk.

The Burden of Inflammation

Last, but not least, inflammation likely plays a major role in linking obesity to cancer. The inflammatory cytokines released by fat cells can harbor the high insulin blood levels that boost the activity of the tumor growth factor IGF-I and increase production of aromatase, which raises estrogen levels.

Fat tissue can also more directly cause cancer or its progression by releasing excessive amounts of tumor necrosis factor (TNF) α and interleukin-6 (IL-6). In animal models or in vitro studies of liver or endometrial cancer, researchers have linked high circulating levels of these cytokines to activation of the tumor-promoting transcription factor STAT3. High circulating levels of TNFα and IL-6 are also tied to increased risk of colon cancer or its precursor lesions and to a higher overall cancer death rate. Fat tissue also releases the enzymes tumors use to invade other tissues and metastasize, such as matrix metalloproteinases.

Researchers continue to unravel the connections between obesity and cancer, with explorations at the population, cellular, and biochemical levels. Nevertheless, enough evidence has amassed that both the International Agency for Research on Cancer and the World Cancer Research Fund have concluded that obesity heightens the risk of esophageal, pancreatic, colorectal, postmenopausal breast, endometrium, gall bladder, and kidney cancers.

Weighty Implications

A major implication of the findings that obesity boosts cancer risk by fostering insulinemia is that T2DM drugs, such as metformin, might lower the likelihood of developing cancer. Several studies show this to be the case.[1] Metformin might also improve cancer survival. A large study at the National Institutes of Health (NIH) is currently exploring this in breast cancer patients.[2]

Another ramification of the ties between corpulence and cancer is that 20%–25% of all cancers might be averted by avoiding being overweight and inactive, researchers estimate. Experts are also raising the alarm that the current obesity epidemic, which afflicts both children and adults in this country, might evolve into a cancer epidemic if nothing is done to stop it. About two-thirds of adults and close to one-fourth of children in the United States are overweight or obese, putting them at increased risk for cancer.

"When you hear a discussion of the importance of obesity in health, it's almost always linked to heart disease and diabetes. But the threat of developing certain kinds of cancers due to obesity could [further] drive people's incentive to get into a healthier weight class," said Harold Varmus, M.D., director of the NIH's National Cancer Institute, at a recent Institute of Medicine meeting. ■

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References and Resources:

1. Please see "Evidence of Less Cancer in Metformin Patients," on page 16 of the February 2011 issue of *Endocrine News* at *www.endo-society.org/endo_news/endo_news_past.cfm*.
2. *http://clinicaltrials.gov/ct2/show/NCT01101438*

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