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CANCER ... HOW EXTRA POUNDS BOOST YOUR RISK

The list of cancers in the U.S. related to obesity is growing alarmingly. How much of a spare tire do you need before your risk climbs? It depends. For some cancers, risk starts to rise even before you cross the line on the body mass index table that defines "overweight." With breast, colon and endometrial cancer, you can see an increase in risk at the high end of the normal-weight range compared to the low end. Fat tissue isn't just dormant storage space ... it's an active organ, releasing and receiving signals from other organs. So far, there are three main theories to explain how those signals may help turn healthy cells into tumors.

The Insulin Pathway. Insulin is the hormone that allows blood sugar to enter cells, where it is either burned for energy or stored as fat. If, however, you have too many overstuffed fat cells, they can become resistant to insulin. It's as though the cells were trying to shut the door that would let in even more sugar. With insulin losing its punch, the pancreas ramps up its output of the hormone. If you have more or bigger fat cells, the pancreas is forced to produce more insulin. High insulin levels are especially likely if you have what experts call "central obesity" (visceral fat located underneath your stomach muscles) ... an apple-shaped body with a big waist instead of the pear-shaped people with big hips. It is clear that insulin resistance increases the risk of diabetes and heart disease, and now cancers of the colon, liver, pancreas and kidney and joining the ranks. How? Here's what researchers do know about cancers linked to the insulin pathway.

1. **Liver.** "Peripheral fat" in the thighs and hips, where a lot of women carry their fat, is not that metabolically active. On the other hand, the "visceral fat" around the waist is constantly sending out signals that promote inflammation or growth elsewhere in the body. (Inflammation, which is often outwardly invisible, is the immune system's attempt to fight off and repair the damage caused by germs, irritants or other insults.) Many people don't realize that once you get beyond a certain level of obesity, fat starts to infiltrate muscle and organs like the liver. A fatty liver starts out benign, but it can lead to cell injury, scarring and inflammation. It can progress from fatty liver to hepatitis to cirrhosis to liver cancer.
2. **Colon.** Colon cancer isn't rare. It kills more non-smokers than any other cancer. The National Institutes of Health did a study which tracked more than 300,000 men and 200,000 women for five years, and the heaviest men had twice the risk of colon cancer, while the heaviest women had a 50% increase in risk. The risk increases even for people who are mildly overweight. Why does obesity seem to matter more in men than women? Fat around your waist is the culprit; men are more likely to gain weight there; a big belly often goes hand in hand with excess insulin; and the data linking insulin to risk is stronger for colon than for any other cancer!
3. **Pancreas.** Pancreatic cancer is deadly. Only one in five patients is alive one year after diagnosis, and only one in 25 survives five years. The only known risk factors are cigarette smoking, diabetes, and obesity ... and, in most studies, being obese doubles the risk. It's still not clear how excess fat leads to pancreatic tumors, but most researchers feel it's probably a consequence of sustained higher levels of glucose and insulin in the blood. Inflammation may also play a role because people who are obese have higher levels of inflammation. Again, it's the visceral fat cells deep in the belly that appear to be at fault. Those fat cells are different ... they are actively causing trouble.
4. **Kidney.** Although kidney cancer accounts for only about 2% of cancer deaths, the incidence is rising in the U.S. and worldwide. Smoking, diabetes, high blood pressure, and obesity all seem to raise the risk, but it's not clear if a large waist matters more than a large number on the bathroom scale. In many studies, excess fat anywhere in the body raised the risk, but in the Women's Health Initiative, which tracked about 140,000 U.S. women for nearly eight years, those with the largest waists had double the risk. Central obesity was the strongest risk factor in these women. What's more, U.S. women who had

lost or gained over 10 pounds more than 10 times during their lifetime had a 2-1/2% times greater risk of kidney cancer than those with stable weights. To quote Karen Margolis, of the University of Minnesota who co-authored the Women's Health Initiative Study, "It appears that weight cycling had a pretty strong relationship with kidney cancer, particularly at the extreme ... but we don't know why."

The Estrogen Pathway. If you're overweight but don't carry the extra pounds in your waist, are you off the hook? No way. Fat—whether it's around your hips, thighs, waist or wherever—produces steroid hormones like estrogen. Another main way that obesity can raise the risk of cancer is through the estrogen pathway. In premenopausal women, estrogen comes largely from the ovaries. After the ovaries stop functioning, the primary source of estrogen production is adipose (fat) tissue ... and estrogen is associated with endometrial and breast cancer.

1. **Breast.** The risk of postmenopausal breast cancer rises by 30% in overweight women and 50% in obese women. For years, researchers couldn't detect the link because they didn't separate women who take estrogen pills from those who don't. Weight is not related to breast cancer in postmenopausal women who take hormones because the pills raise estrogen levels—and the risk of cancer—whether the women are skinny or fat. The sharp decline in the number of women taking postmenopausal hormones means that weight matters to an increasing segment of the population. More than other cancers, postmenopausal breast cancer is related to how much weight you gain as an adult. That's in part because obesity may *lower* the risk of breast cancer in premenopausal women because obesity so often impairs a woman's ability to ovulate. So the woman with the highest risk was normal weight with regular periods when she was young and became obese when she got older. Excess adiposity is an important contributor to breast cancer risk in postmenopausal women, especially for tumors that are most likely to spread.
2. **Uterus.** Cancer of the endometrium (the lining of the uterus) is twice as likely in overweight women and 3-1/2 times more likely in obese women. This was the first cancer recognized as related to obesity. It is known that endometrial cancer is associated with estrogen that's unopposed by progestin. Decades ago, researchers found that women who took estrogen pills had a higher risk of uterine cancer, but the risk disappeared in women who took estrogen combined with progestin. More recently, researchers have detected a higher risk among women with central obesity. In a study of 223,000 European women, the risk of uterine cancer in those with at least a 35-inch waist was 76% higher than in those with a waist smaller than 32 inches. Once you get to some level of obesity, you're going to have a certain amount of central adiposity no matter where you carry your weight.

Local Impact. For some cancers, obesity seems to boost risk because it leads to problems in nearby tissues, rather than by altering circulating hormones. For example:

1. **Esophagus.** Two distinct cancers show up in the esophagus, and with a five-year survival rate of 16%, both are deadly. First, there's squamous cell carcinoma (which is common in alcoholics, who are often underweight), whose rates have leveled off, and then there's adenocarcinoma (common in the overweight population), whose rates are on the upswing, and more so in men than in women, but no one knows why.
2. **Gallbladder.** The gallbladder is a pear-shaped organ below the liver that collects and stores bile (a fluid made by the liver to digest fat). In about 1/4 of all cases, gallbladder cancer is found early, usually when the organ is removed for other reasons, and the five-year survival rate is 80%. While gallbladder cancer is rare, excess weight accounts for more than one-third of all cases in the U.S. How? Obesity is associated with gallbladder stones; the stones provide a local inflammatory environment, which sets the stage for cancer.

Back in 2002, the International Agency for Research on Cancer concluded that people who are overweight or obese have a higher risk of the following five cancers: breast, colon, esophagus, kidney and uterus. More recently, an expert at the American Cancer Society (Eugenia Calle) said she would add gallbladder, liver, pancreas, and advanced prostate cancers to this list, that extra pounds account for an estimated 20% of all cancer deaths in the U.S., and that the percentage is growing because Americans are growing! We all have the power to turn this trend around one human being at a time.