

# OBESITY AND CANCER

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## INTRODUCTION

The relationship between obesity and cancer is complex because the etiology of cancer is multifactorial and includes contributing factors such as genetic inheritance, exposure to chemicals and environmental hazards, radiation, smoking, viruses, and autoimmunity. Nonetheless, there is growing evidence that obesity increases both the incidence and the mortality of many malignancies.

Visceral fat adipocytes secrete multiple biologically active polypeptides that act by endocrine, paracrine, and autocrine mechanisms. Six of these adipocytokines promote angiogenesis, while only one, adiponectin, is inhibitory and has been shown to inhibit tumor growth in animals.<sup>1,2</sup> Since the importance of angiogenesis in the development and progression of breast cancer is well established, it is plausible that obesity-related increases in the production of adipocytokines and a reduction in adiponectin may adversely affect breast cancer outcomes.

Other theoretical mechanisms include obesity-related inflammatory cytokines, altered immune response, and hypertension, as well as lipid peroxidation for renal cancer and acid reflux for esophageal adenocarcinoma.

## CLINICAL EVIDENCE

The recent evidence for the connection between obesity and cancer comes from two important studies which examined the relationship between body mass index (BMI) and both the incidence and the mortality of cancer in very large numbers of patients.<sup>1,2</sup>

The first study, published in 2003, prospectively examined more than 900,000 U.S. adults from 50 states and Puerto Rico who were free of cancer when they were first enrolled in 1982 at an average age of 57.<sup>2</sup> Body Mass Index was calculated from weight and height at entry, and they were categorized into 5 groups from normal to grade IV overweight. Other co-variables assessed included age, race, smoking status, education, alcohol use, physical activity, aspirin use, estrogen replacement therapy, and dietary habits. A subgroup of 376,000 non-smokers was identified.

Importantly, follow-up until 1998 was nearly complete, with over 99% of deaths ascertained; 93% were linked to the

National Death Index. Overall, 24% of the entire group had died, with 57,000 deaths from cancer in the total group and 17,000 cancer deaths in non-smokers. Thus, the numbers in all groups were quite large, and provided important statistical validity.

## CANCER MORTALITY AND BODY MASS INDEX

In men with BMI 35.5-39.9, the relative risk of death from any cancer was 1.20 (95% CL 1.08-1.34); for men with BMI > 40, the relative risk rose further to 1.52 (95% CL 1.13-2.05). Linear relationships between BMI and death rates were seen for cancers of the esophagus, stomach, gallbladder, pancreas, colon and rectum, kidney, and prostate, as well as for non-Hodgkins lymphoma, multiple myeloma, and leukemia. Interestingly, there was an inverse ratio between BMI and death rates from lung cancer.

Among women with BMI > 40 the relative risk for death from any cancer was 1.62 (95% CL 1.40-1.87). These risks were noted for colorectal, gallbladder, pancreatic, cardiac, uterine, cervical, ovarian, renal cancers, and for non-Hodgkins lymphoma. The highest relative risk of 6.2 was seen in uterine cancer. As in men, an inverse association was observed between BMI and death rates from lung cancer.

When the analysis was restricted to non-smokers, the increased risk in the most overweight was magnified, while the inverse relationship to death from lung cancer disappeared. The authors point out that smoking profoundly alters the relationship between BMI and many causes of death, and the most valid analyses of the influence of obesity on the incidence and mortality of cancer are derived from studies of those who never smoked.

The proportion of all deaths from cancer attributable to obesity was estimated to range from 4.2-14% in men and 14.3-19.8% in women. (The higher numbers in the range are for non-smokers.) Compared with people of normal weight, the heaviest men and women had death rates from all cancers that were respectively 52% and 62% higher. Using the higher numbers in the range, the authors estimated that 90,000 cancer deaths per year could be avoided if every adult maintained a BMI under 25 throughout life.

An additional recent study from Europe searched Medline and Embase without language restrictions for studies in humans of the association between body weight and cancer. They reviewed 221 data sets covering 282,137 cases of diagnosed cancer and 133,000,000 person years of follow-up.<sup>1</sup>

In men, increasing BMI was strongly associated with esophageal adenocarcinoma, as well as cancer of the colon and kidney. Weaker associations were seen with melanoma, myeloma, non-Hodgkins lymphoma, leukemia, and rectal cancer. In women, a 5 kg/m<sup>2</sup> increase in BMI was associated with a higher mortality for cancer of the endometrium, gallbladder, and kidney, as well as esophageal adenocarcinoma. Weaker associations were seen with thyroid, post menopausal breast, pancreas, and colon cancer and non-Hodgkins lymphoma. Once again, increasing BMI was negatively associated with lung cancer, as smokers tend to have lower BMIs.

#### INCIDENCE OF BREAST CANCER AND BODY MASS INDEX

The above studies looked mainly at mortality from cancer rather than just its incidence. Other studies have suggested that excessive weight can be correlated with an increased incidence of breast cancer as well as with more advanced stages at diagnosis. In addition to the causative factors discussed above, a specific factor for breast cancer in heavier women is a higher level of circulating estradiol, which results from the conversion of estrogen precursors to estrogen by adipose tissue.<sup>3</sup>

The association between breast cancer and BMI varies among different geographical regions. Increased BMI is associated with an increased risk of pre-menopausal breast cancer in Asia-Pacific populations, but not in other regions. Asian populations also have the strongest association between increased BMI and post-menopausal breast cancer.

In Western populations, higher weight and BMI as well as post menopausal weight gain have been associated with a higher risk of breast cancer,<sup>4</sup> and the greatest influence of weight is seen in non-users of hormone replacement therapy.<sup>3</sup> The increase in risk is considerable: weight gain of >10 lbs is associated with an 18% increase in risk, and BMI > 33 is associated with a 27% increase. Post menopausal women who were not using HRT and lost

more than 10kg had a 57% lower risk of breast cancer<sup>3</sup>. Similarly, regular physical exercise reduces the risk of post-menopausal breast cancer.

In contrast, most studies show an inverse relationship between obesity and pre-menopausal breast cancer. This finding is likely related to the fact that high BMI is associated with irregular and anovulatory menstrual cycles characterized by decreased levels of estrogen and progesterone.

There have been studies of fat intake and the risk of breast cancer, but they are conflicting and inconclusive. In premenopausal women there may be a minimal benefit of low fat diets. In women diagnosed as having breast cancer, a reduction in fatty food intake has been associated with a reduction in deaths from cardiac causes, but not from breast cancer.

#### COLON CANCER

Obesity confers a 1.5 fold increase in the risk of developing colon cancer as well as a higher likelihood of dying from colon cancer.<sup>2,4</sup> As with breast cancer, recreational physical activity, which obviously has an inverse relationship with obesity, substantially reduces the risk of colon cancer. The protective effect is strongest for cancer of the distal colon. The postulated mechanisms of action include decreased GI transit time, altered prostaglandin levels, and changes in bile acid metabolism.

While circulating estrogen levels are felt to have a role in breast cancer, insulin resistance and hyperinsulinemia are speculated to be a key to the relationship of obesity to cancer in general. The increased levels of circulating insulin result in increased levels of insulin-like growth factor,<sup>2</sup> which can affect mitogenesis and apoptosis.

#### CONCLUSION

Multiple large studies have clearly shown an adverse impact of obesity on the risk of developing as well as dying from most common cancers except for lung cancer. This risk is independent of most other risks such as smoking, genetics, and environmental chemical exposure. Finally one must note that obesity is just one of many factors and variables that impact the causation of cancer and that there have been no studies performed to date that demonstrate a reduction in the incidence or mortality from cancer resulting from reducing the prevalence of obesity in a given population.

#### REFERENCES

1. Rapp, K., Schroeder, J., Klenk, J., Stoehr, S., Ulmer, H., Concin, H., Diem, G., Oberaigner, W., Weiland, SK., Obesity and Incidence of Cancer: A Large Cohort Study of Over 145, 000 Adults in Austria. *British Journal of Cancer* 2005; 93: 1062-1067
2. Renehan, A., Tyson, M., Egger, M., Heller, R., Zwahlen, M. Body-Mass Index and Incidence of Cancer: A Systematic Review and Meta-Analysis of Prospective Observational Studies. *Lancet* 2008; 371: 569-78.
3. Costanza, M., Chen, W., Epidemiology and Risk Factors for Breast Cancer. 2009; uptodateonline.com
4. Martinez, M., Giovannucci, E., Spiegelman, D., et al. Leisure-Time Physical Activity, Body Size and Colon Cancer in Women. *J. National Cancer Institute* 1997;89:948-955
5. Calle, E., Rodriguez, C., Thun, M., Walker-Thurmond, K. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. *N Engl J Med* 2003; 348: 1625-38.
6. Li, D., Morris, J., Liu, J., et al. Body Mass Index and Risk, Age of Onset, and Survival in Patients With Pancreatic Cancer. *JAMA* 2009; 301: 2553-2561

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